Draft Comparative Effectiveness Review

Number XX

Treatments for Fibromyalgia in Adult Subgroups

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Treatments for Fibromyalgia in Adult Subgroups

Structured Abstract

Objective. We conducted a systematic literature review of clinical trials to assess the comparative effectiveness of treatments for fibromyalgia in subgroups of highly affected or clinically complex adults. We focused on complex patient subgroups rather than overall treatment effects to complement a large systematic review being conducted on fibromyalgia treatments at McMaster University.

Data sources. We searched Medline, EMBASE, PsychInfo, AMED, and the Cochrane Clinical Trials Registry (CCTR) plus reference lists of included studies and recent systematic reviews.

Methods. Two investigators screened abstracts of identified references for eligibility (adults, with fibromyalgia, examined treatment effects, had a control group and assessed outcomes at least 3 months after treatment initiation). Full text articles were reviewed to identify outcomes reporting for at least one adult subgroup: women, older or obese adults, individuals with coexisting mental health conditions, high severity or longer fibromyalgia duration, multiple medical comorbidities, or other chronic pain conditions. Primary outcomes included pain, symptom improvement, function, participation, fatigue, sleep quality, and health-related quality-of-life. We extracted data, assessed risk of bias on individual studies, and evaluated strength of the body of evidence for each comparison and outcome.

Results. We identified 19 randomized clinical trials (RCTs), 8 pooled analyses of patient-level RCT data and 4 observational studies that met inclusion criteria; over half were drug trials. Adults with fibromyalgia and major depressive disorder (MDD) were studied most often; subgroup outcomes by age, sex, race and anxiety were studied less often. Most drug trials examined duloxetine effects on pain and global improvement. Trial duration was typically 3 months; no study lasted more than 1 year. Low strength of evidence subgroup treatment effects were generally small, beneficial, and similar to nonsubgroup effects in direction and magnitude. Treatment-by-subgroup interactions were not significant in nearly all comparisons. Only one RCT and five pooled RCT analyses displayed subgroup data for outcomes; most interaction results were reported in text. Placebo group improvements were considerable but typically not discussed. Losses to followup were generally high and dropout reporting was not subgroup-specific. Adverse effects were reported for subgroups in only one pooled analysis and were similar in the MDD subgroup. Subgroup samples were small except in pooled analyses; studies were not powered to detect subgroup effects.

Conclusion. Limited, low strength of evidence for subgroup outcomes in adults with fibromyalgia suggests that complex patient subgroups do not have differential treatment effects compared with other adults with fibromyalgia. Overall treatment effects were small and even less when substantial placebo-group improvements were considered relative to treatment effects.

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Executive Summary

Background

Fibromyalgia is a chronic, diffuse musculoskeletal pain syndrome of unknown etiology. It affects mostly adults[1] and is characterized by chronic widespread pain, abnormal processing of and heightened sensitivity to pain, chronic fatigue, sleep disorders, and emotional distress or depression.[1,2] Fibromyalgia reduces quality of life and productivity and is associated with functional disability, lost work time, and increased use of health care services.[1,3-5] Based on diagnostic criteria developed in 1990 by the American College of Rheumatology (ACR), fibromyalgia affects more than 5 million Americans,[6] most of whom are middle-aged women.

The diagnostic criteria for fibromyalgia have evolved[7,8] since their first iteration by the ACR in 1990, which included palpation of myofascial "tender points" during physical examination and the presence of widespread pain for at least 3 months.[9] In 2010 the ACR eliminated the tender point examination criterion, adding physician-rated severity in two scales, the Widespread Pain Index and the Symptom Severity Scale, and requiring symptoms for at least 3 months and the absence of another disorder that would account for the symptoms.[7,10] A survey version of the 2010 ACR criteria was also released for research purposes in 2011 that replaced physician estimates of somatic symptom severity with a patient-generated summary score derived from three self-reported symptom domains.[8,11] The 2010 ACR preliminary diagnostic criteria compared with those published in 1990 capture a broader population of fibromyalgia patients that affects prevalence estimates and patient heterogeneity in more recent studies.[10,12,13]

As a syndrome, fibromyalgia has no single etiology, and available pharmacological and nonpharmacological modalities help mitigate symptoms and improve function.[1] Current treatments are most often multifaceted and involve multidisciplinary approaches and providers. Treatment goals are to mitigate diffuse musculoskeletal pain, maximize physical and cognitive function, optimize patient self-management and self-efficacy, and manage comorbid medical and psychiatric disorders. Treatment components may include pharmaceutical therapy, exercise programs, cognitive behavioral therapy, patient education (self-management, sleep hygiene, importance of exercise, etc.), and the treatment of comorbid medical and mental health conditions.[1,14] Also common are complementary and alternative medicine (CAM) approaches.[14,15] Pharmacologic interventions include both FDA-approved medications specifically for the treatment of fibromyalgia and other FDA-approved drugs not specifically approved for the management of fibromyalgia symptoms in the United States. Since 2007 three oral medications are FDA-approved specifically for fibromyalgia: pregabalin, duloxetine, and milnacipran. In addition, numerous drugs that have been FDA-approved for other conditions are currently used as primary or adjunctive therapeutics in patients with fibromyalgia ("off-label" usage), such as antidepressants, analgesics, opioid analgesics, anti-inflammatories, and skeletal muscle relaxants. A wide array of nondrug treatments are also used to manage pain and other symptoms of fibromyalgia, often in combination. Categories of nonpharmacological treatments for fibromyalgia include psychological, physical (active or passive), multicomponent, lifestyle modifications, and other therapies including nutraceuticals, with the goal of improving physical function, endurance, and self-efficacy in fibromyalgia management, both short and long-term.

Many clinical trials suggest a modest benefit from treatments for a general population of fibromyalgia patients.[14,16] Less is known, however, about the efficacy and comparative effectiveness of these treatments for highly affected or clinically complex subgroups of adults

(defined by number and type of coexisting syndromes or conditions, severity of pain or impairment at baseline,[7] presence of a mood or other mental health disorder, primary complaint at baseline, or demographic or other related factors). This systematic review provides information for both patients and providers on treatment outcomes in fibromyalgia subgroups.

Scope and Key Questions

This systematic review addressed whether specific subgroups would benefit from being treated differently from the general fibromyalgia patient population. McMaster University in Canada is conducting a comprehensive systematic review of randomized clinical trials on interventions for fibromyalgia in adults.[17] Our systematic review complements the McMaster work by adding unique information on outcomes in fibromyalgia patient subgroups and by including observational literature. The patient subgroups were chosen *a priori* with input from experts and other stakeholders to include the following subgroup categories: women,[18-22] older[23,24] or obese[25] adults, individuals with coexisting mental health conditions,[1,6,26-28] those with high severity[28-31] or longer fibromyalgia duration,[32] multiple medical comorbidities,[1,32,33] or other chronic pain conditions.[1,6,14,27,34] Additional subgroups were included as found in the literature. We limited our analysis to studies of individuals age 18 or older that compared treatments for fibromyalgia in subgroups of adults who were followed for at least 3 months after treatment initiation because fibromyalgia is largely a chronic condition in adults. We included only clinical studies with control groups. Studies could potentially assess the effects of a treatment within a given subgroup, or they could contrast the effects in that subgroup to those on other patients.

The following two key questions were the focus of this systematic review:

Key Question 1 (KQ 1)

What are the efficacy and comparative effectiveness of treatments for fibromyalgia in each of these specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Persons with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Individuals with other significant chronic pain conditions (e.g., low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Key Question 2 (KQ 2)

What are the harms of treatments for fibromyalgia in each of these specific adult subpopulations?

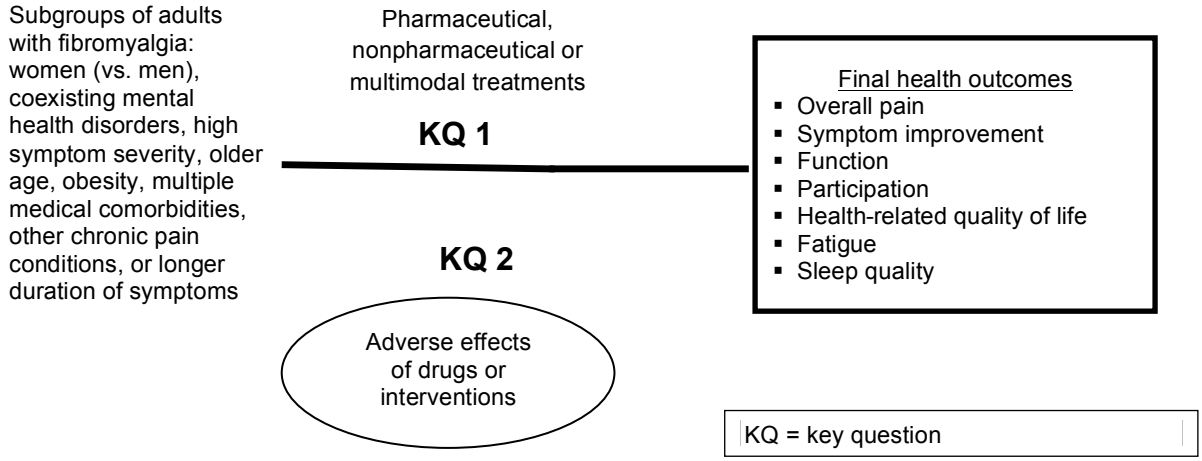
- Women
- Individuals with coexisting mental health conditions

- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Individuals with multiple medical comorbidities
  Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  Other comorbidities
- Individuals with other significant chronic pain conditions (e.g., low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Analytic Framework

The analytic framework for the Key Questions is depicted in Figure ES1 below. The figure illustrates how the use of pharmaceutical, nonpharmaceutical, or multimodal treatments may improve outcomes for adults with fibromyalgia.

Figure ES1. Analytic framework for treatments for fibromyalgia in adult subgroups



Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the ARHQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm).

Literature Search Strategy

We used bibliographic databases to identify randomized controlled trials, systematic reviews, and observational studies with control groups published from 1985 to the present on treatments for adults with fibromyalgia. Relevant bibliographic databases for this topic included Ovid MEDLINE®, Embase, Ovid PsychINFO, and AMED (Allied and Complementary Medicine) and the Cochrane Central Register of Controlled Trials (CENTRAL). We supplemented

bibliographic database searches with backward citation searches of highly relevant systematic reviews.

Eligibility

We included randomized clinical trials (RCTs), pooled analyses of individual patient-level RCT data, and observational studies published in English from 1985 to the present that examined one or more treatments for fibromyalgia in adults, utilized a comparator group, and reported treatment outcomes in at least one subgroup 3 months or more after the initiation of treatment. We excluded studies: of drugs not FDA-approved in the United States for any condition; that included patients with different health conditions and did not separately report baseline and outcomes in fibromyalgia patients; that did not use established fibromyalgia diagnostic criteria for subject selection (American College of Rheumatology [ACR][7-9] or Yunus[35] criteria for fibrositis from 1985-1990); or pharmaceutical RCTs where patients were unblinded to treatment for any part of the study.

Two independent investigators independently determined study eligibility, resolved disagreements through discussions (possibly with a third adjudicator) until consensus was achieved. Study selection involved an extensive full text review process to identify adult subgroups, since subgroup reporting was commonly not evident in titles and abstracts.

Data Extraction

We extracted data from included studies into evidence tables by the type of study design that included relevant population, intervention, baseline, and outcomes data on the adult subgroups of interest. Initial data abstraction was quality checked by a second investigator. The final evidence tables are presented in Appendix E of the full report.

Quality (Risk of Bias) Assessment of Individual Studies

The risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design. The two investigators consulted to reconcile any discrepancies in overall risk of bias assessments and, when needed, a third investigator was consulted to reconcile the summary judgment. For RCTs we assessed the risk of bias using a modified Cochrane Risk of Bias tool.[36] We included additional items to assess the credibility of subgroup analysis of individual RCTs based on Sun et al.[37] Overall summary risk of bias assessments for each study were classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.[36] We developed an instrument to assess risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank[38] because concerns about selection bias and blinding make the use of observational studies debatable in comparative effectiveness reviews. We selected items most relevant in assessing risk of bias from observational studies and to foster consistency with the risk-of-bias instrument for randomized controlled trials.[36]

Data Synthesis

We summarized the results into evidence tables and qualitatively synthesized evidence by the type of study (RCT, observational, pooled RCT) for each unique population, comparison, and outcome combination within specific followup time periods. Studies were grouped by

intervention category and then subgroup. We summarized data on pain, fatigue, function, and quality of life. Pooling was planned for outcomes that assessed the same outcome and had comparable scoring characteristics (such as the FIQ[39] and FIQR[40] tools). When subgroup data was provided, we calculated the absolute difference between treated and control groups by subgroup strata for each outcome and assessed whether or not the difference met or exceeded minimal clinically important differences for fibromyalgia patients (if known).

Strength of the Body of Evidence

We evaluated the overall strength of evidence for selected clinical outcomes based on four domains: (1) study limitations (internal validity); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate) with the study limitations domain having considerable importance.[41] Assessing reporting bias was not required.[38] Study limitations were rated as low, moderate, or high according to study design and conduct. The possible strength of evidence grades[41] were:

- High. High confidence that the evidence reflects the true effect. Further research is unlikely to change the estimates.
- Moderate. Moderate confidence that the estimate reflects the true effect. Further research may change estimates and our confidence in the estimates.
- Low. Limited confidence that the estimate of effect lies close to true effect. Further research is likely to change confidence in the estimate of effect, and may change the estimate.
- Insufficient. Evidence is either unavailable or does not permit a conclusion

Applicability

Applicability of studies was determined according to the PICOTS framework. Adults in clinical trials of fibromyalgia treatments may be higher functioning and/or less impaired than the fibromyalgia patient population as a whole to maximize followup. For subgroups, this would not limit applicability but rather limit the number of studies with adequate subgroup inclusion and reporting.

Results

Overview

We included several types of studies. RCTs with mixed patient samples refer to those studies that identified a patient subgroup after randomization (such as adults with fibromyalgia, a proportion of whom had depression). RCTs that selected within particular subgroups (such as sedentary women or postmenopausal women) comprised another group of included studies. We refer to this collection of studies as pure subgroup RCTs. A third type of study was a pooled analysis of individual patient data from several RCTs to report subgroup outcomes. We refer to these as pooled analyses of individual patient data (IPD) from RCTs, or pooled IPD RCT analyses. All such studies investigated pharmaceutical interventions. Finally, observational studies with comparator groups were included.

A complete list of abbreviations and acronyms can be found in the full report.

Results of Literature Searches

We identified 6069 citations from all databases combined. We examined the full text of 499 articles (376 RCTs, 22 pooled analyses of patient-level RCT data, and 101 observational studies) to assess for subgroup reporting. Of those, 31 studies were included in the analysis (Table 4 and Figure 2): 19 RCTs, 8 analyses that pooled IPD from RCTs,[27,42-48] and 4 observational studies.[49-52] The two types of RCTs included 9 studies with mixed patient samples[53-61] and 10 RCTs of pure subgroups.[62-71] Of the 19 RCTs, 9 were placebo-controlled trials. Over half of included studies were drug trials (n=19, 61 percent). All included studies were published in 2001 or later, with the eight pooled IPD RCT analyses all published since 2009. Table A summarizes the included studies by design. The QUORUM diagram for the study selection process and a list of excluded studies are provided in the full report.

Table A. Included fibromyalgia subgroup studies, by study design

Study Design	Count
Randomized clinical trials	9
Randomized clinical trials of pure subgroups	10
Pooled analyses of individual patient data from randomized clinical trials	8
Observational studies	4
Total of included studies for report	31

Key Question 1. Treatment effectiveness in fibromyalgia subgroups

Overview

Given the sparse evidence for specific treatment-subgroup-outcome combinations, we were unable to conduct meta-analyses. Instead, subgroup results are presented in tables in the full report where data for subgroup outcomes were reported (one RCT[55] and five pooled IPD analyses[42-44,47,49]) or in summary tables from articles with text-only reporting of interaction effects. Qualitative summary information for other comparisons is provided in the text below. A basic map of the included studies that assessed specific treatment-subgroup-outcomes combinations is provided in the full report as are basic study information tables for all included studies (Appendix Tables E4-E7).

Key Points

- Limited existing literature on highly affected or clinically complex subgroups of adults with fibromyalgia provides low strength of evidence that patient subgroups do not experience significantly different fibromyalgia treatment effects relative to other adults with fibromyalgia.
- In studies with mixed patient samples, subgroup treatment effects were generally small, beneficial, and paralleled nonsubgroup effects in direction and magnitude.
- Common study issues that bias subgroup study conclusions include high overall attrition that was not reported for subgroups or by treatment groups, small subgroup sample sizes, studies not powered to detect subgroup effects and selective reporting of outcomes.
- Adults with fibromyalgia and major depressive disorder were assessed most often, especially the effects of duloxetine on pain. Less information is available on potentially differential treatment effects by age, sex, race, or other subgroups.
- Few studies assessed outcomes beyond 3 months. The longest trial was 1 year (psychotherapy).

- Outcomes of statistical tests to assess whether treatment effects differ within select subgroups (treatment-by-subgroup interaction results) are most commonly reported in text, or not reported; presentation of data was rare (one RCT), except in pooled IPD RCT analyses.
- Most individual clinical studies were not sufficiently powered to detect differences in treatment effects in subgroups, if they existed

Pharmacological Therapies

The majority of included studies reported the effects of pharmacological therapies on pain and other outcomes in subgroups of adults with fibromyalgia. All eight pooled analyses of patient-level RCT data were pharmaceutical investigations. Duloxetine effects were studied most often.[42-44,53-57] Subgroups examined in pharmacologic studies included depression (11 studies), age (5 studies), sex (5 studies), anxiety (3 studies), obesity/Body Mass Index (BMI) (2 studies), and medical comorbidities (1 study). Additional subgroups found in drug studies were race (3 studies), baseline fatigue level (1 study), postmenopausal women (2 studies), and 1 study that used baseline Visual Analog Scale (VAS) pain ratings for subgroup definition.

The literature set for pharmaceutical interventions is comprised exclusively of high risk of bias studies due to high attrition, lack of attrition reporting for subgroups or treatment groups, and small subgroup sample sizes in nonpooled analyses (Appendix C). Overall attrition in drug trials ranged from 4 percent in one off-label international trial[63] to 47 percent,[55] with most studies having 25 to 40 percent overall attrition. Only 2 off-label pharmaceutical trials reported overall attrition of less than 25 percent.[62,63]

At least 16 of 19 drug trials were industry funded among those where funding source was identified (Appendix Tables E4-E7 and E13-E16). Industry involvement in studies included data management, statistical support, manuscript drafting, construction of figures and tables, and study management. Corresponding and other authors in pharmaceutical trials were often industry employees.

Subgroup Outcomes

Comorbid Mental Health Conditions

Depression

Adults with fibromyalgia and major depressive disorder (MDD) or history thereof were the most frequently assessed subgroup for treatment interactions in pharmaceutical studies, and across all other types of treatments. Ten drug studies (seven RCTs, six FDA-approved, one off-label, two pooled IPD RCT analyses, and one observational study) assessed treatment-by-MDD interactions on the outcomes of pain, global improvement, fibromyalgia impact, and depression. One additional pooled IPD RCT analysis reported stratum-specific changes in pain rather than an interaction effect (Table 6).[47]

Pharmacologic treatments did not appear to have differential effects in adults with both fibromyalgia and depression. Pain was the most common outcome assessed in adults with fibromyalgia and comorbid depression, including five RCTs (four of duloxetine[53,55-57] and one of milnacipran,[58]) and two pooled RCT analyses,[43,44] both of duloxetine. All treatment-by-MDD interactions on pain as an outcome in the pharmacologic studies we examined were either not significant or not reported. Five different measures were used to assess pain in the MDD

subgroup, with the BPI average pain severity score being utilized most often (Appendix Tables E8 and E9). For pain, one high risk of bias RCT by Russell et al.[55] and one pooled IPD RCT analysis of four high risk of bias RCTs[44] of duloxetine trials presented data on MDD subgroup outcomes for the BPI average pain severity score (Tables 7 and 8). The interaction result was not reported; the text implies that it was not significant.[55] The differences between treated and control patients with or without MDD did not exceed minimal clinically important differences in either study, as determined for adults with fibromyalgia.[72]

The RCT by Russell et al. 2008[55] also displayed MDD subgroup data for the Patient Global Impression of Improvement (PGI-I), a 7-point scale ranging from 1 (very much better) to 7 (very much worse).[73] Study authors noted similar improvements in PGI-I in treated versus controls regardless of MDD status. However, dropouts were assigned a PGI-I score of 4 (corresponding to no change) for the analysis, which assumed no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases[55] (Table 7).

All other treatment-by-MDD interaction results were reported in article text only, with or without p-values. All treatment-by-MDD interactions were not significant or not specifically reported (Tables 9 and 10).

The FIQ and FIQ pain subscales were examined as primary outcomes in two RCTs, one of duloxetine[57] and one of fluoxetine.[59] Both treatment-by-MDD interactions on the FIQ pain subscales[57,59] and FIQ total scores[57] were not significant.

For the Patient Global impression of Improvement (PGI-I) outcome, the duloxetine-by-MDD interaction in two RCTs was not statistically significant[54] or not reported.[55]

One RCT assessed changes between treated and placebo-controlled patients on the Hamilton Depression Rating scale but within the MDD stratum;[55] changes from baseline to 6 months in treated versus controls were not significantly different (Table 11).

One observational study of milnacipran was a post-hoc analysis of RCT data that stratified by baseline Beck Depression Inventory scores to assess improvement in VAS pain scores; no formal statistical analysis was conducted for subgroup effects.[49]

These reported results should be considered along with issues common to this set of studies. At baseline, MDD subgroup sample sizes were small in all RCTs, excluding the pooled IPD RCT analyses. The number of patients with MDD at final followup in both treatment and control groups were usually not determinable due to incomplete reporting of denominator values and dropouts per subgroup or by treatment groups after baseline. The lack of denominator values after baseline was common in both RCT and pooled analyses.

The collective strength of evidence for the beneficial effects of duloxetine on pain (BPI average pain score), global improvement (PGI-I) and impact of fibromyalgia (FIQ total score) was low for all three outcomes (Table 12).

Other Subgroups

Anxiety

The interaction of duloxetine treatment and generalized anxiety disorder (GAD) on the outcomes of BPI average pain and global improvement (PGI-I) were considered in 2 RCTs[53,54] for a total of 63 GAD-affected patients. Both interaction terms were not significant. One additional pooled IPD RCT analysis of pregabalin reported stratum-specific changes from baseline in a weekly average pain rather than an interaction effect.[47]

Age

Five pharmaceutical studies examined potential age-related differences in treatment effectiveness in adults with fibromyalgia: three high risk of bias RCTs[53-55] and two pooled analyses of IPD from high risk of bias RCTs.[42,48] Four of five studies tested duloxetine effects (three RCTs[53-55] plus one pooled IPD RCT analysis[42]) and one pooled analysis examined pregabalin.[48] All investigations reported 3-month outcomes; only one mixed sample RCT also assessed 6-month outcomes.[55] Treatment-by-age interactions were not significant for pain (Brief Pain Inventory [BPI] average pain severity), global improvement (PGI-I) or on the Fibromyalgia Impact Questionnaire (FIQ) stiffness subscale. The pooled IPD analysis by Bennett, et al.[42] provided pooled data for nonsignificant differences in the effect of duloxetine on dichotomized age categories. The pregabalin article provided summary comments of effect only.[48]

Sex

Seven pharmacologic studies reported subgroup outcomes by sex. Five studies examined sex as a treatment effect modifier: four high risk of bias RCTs[53-55,57] plus one pooled IPD RCT analysis.[48] All five studies assessed the effects of duloxetine. Followup was 3 months in all studies; one RCT also assessed 6-month outcomes.[55] Three of four RCTs reported that treatment-by-sex interactions were not significant for BPI average pain and Patient Global Improvement (PGI-I). One high risk of bias RCT (Arnold, 2004[57]) found significant treatment-by-sex interactions on nonprimary outcomes, with statistically significant improvement in pain (BPI average pain) (p=0.046) and the Sheehan Disability Scale (p=0.007) in women verses men. A pooled analysis of four RCTs reported greater pain reduction in females versus males in text but did not provide useable interaction results.[48]

Two additional high risk of bias pure subgroup RCTs assessed pharmacologic effects in patient samples that were limited to postmenopausal women.[62,63]

Race

Treatment-by-race interactions were assessed in three RCTs, all of duloxetine. The outcomes included BPI average pain severity[53] and global improvement (PGI-I).[54,55] The interaction was not significant in two of three RCTs. However, Arnold et al. 2012[53] reported a significantly greater mean decrease (improvement) in BPI average pain in non-white (versus white) patients taking duloxetine 30mg/day.

Obesity

Two pooled IPD analyses examined the outcomes of stiffness (FIQ subscale) and weight loss for subgroups determined by BMI at baseline: one of duloxetine and one of milnacipran. All input RCTs for these pooled IPD analyses were high risk of bias studies. The duloxetine pooled IPD analysis[42] assessed whether treatment effects on stiffness, measured by the FIQ stiffness subscale, varied by BMI. The 3-month outcomes were reported, stratified by BMI (normal, overweight, obese, and morbidly obese) (Table 8). The treatment-by-BMI interaction effect of duloxetine on changes in the FIQ stiffness measure was not significant. However, the small differences between treated and placebo-controlled patients in changes in FIQ stiffness from baseline decreased with increasing levels of BMI; only baseline enrollment numbers were reported and no power calculation was provided for the subgroup comparison. None of the differences between treated versus placebo within BMI strata met MCID (13 percent change) for the FIQ stiffness subscale.[29]

Fatigue

Bradley et al.[43] conducted a pooled analysis of IPD RCT data to determine whether the effects of duloxetine on the BPI average pain score varied by baseline level of fatigue as measured by the FIQ tiredness subscale. Subgroup data were presented (Table 8). The interaction term was not significant ($p>0.1$). Differences between treated and control subjects in the change in BPI average pain within tiredness strata did not meet MCID.

Other Subgroup Outcomes

Within-subgroup changes from baseline in pain were reported by Bhadra et al.[47] in a study of varying doses of pregabalin, although no interaction effects were assessed (Table 6). No other subgroups were separately reported in included studies.

Strength of Pharmaceutical Evidence

The strength of evidence was low for the effectiveness of all pharmaceutical interventions in alleviating symptoms of fibromyalgia syndrome. Individual clinical trials all had high risk of bias (Appendix Tables E10-E12).

Physical Treatments

Five pure subgroup RCTs examined the effects of physical interventions[64-66,68] or dietary changes[67] on outcomes in subgroups of adults with fibromyalgia. Three of five RCTs examined exercise interventions.[64,66,68] Two studies had a moderate risk of bias;[64,65] all others were high risk of bias. Sample sizes ranged from 21 to 83 adults at enrollment, for a total of 231 subjects across all 5 studies.

The strength of evidence was insufficient to compare treatment outcomes by physical interventions in these pure subgroup RCTs. (Appendix Table E10).

Psychological Therapies

Four studies examined the effects of psychological therapies in subgroups of adults with fibromyalgia: one mixed-sample RCT,[60] two pure subgroup RCTs,[69,70] and one observational study.[51] Study duration ranged from 3 months to 1 year, which was the longest followup of any studies included in this report. Sample sizes were small. All assessed unique outcomes in disparate subgroups and all were high risk of bias studies. The strength of evidence was insufficient to compare subgroup treatment effects for psychological interventions. (Appendix Tables E10 and E11).

Mixed Types of Treatments

Three studies assessed combination therapies, and each study had a high risk of bias. The strength of evidence was insufficient to compare treatment outcomes for mixed types of fibromyalgia treatments. All three studies assessed unique treatment-subgroup-outcomes combinations, and all had a high risk of bias (Appendix Tables E10 and E11 of the full report).

Key Question 2. Adverse treatment effects in fibromyalgia subgroups

The clinical trial literature on adults with fibromyalgia that reported on subgroup treatment effects was nearly devoid of adverse effect (harms) reporting for subgroups.

Key Points

- Harms were rarely reported by subgroup.
- There was insufficient evidence to determine whether or not adverse effect of treatments for adults with fibromyalgia vary in adult subgroups or whether subgroups experience atypical harms for a given treatment.
- When reported, adverse effects did not markedly differ in subgroups compared to the general patients.

All Studies

None of the nine mixed sample RCTs with subgroup outcomes separately reported adverse effects (AEs) by subgroups.[53-61] Of the ten pure subgroup RCTs, only three reported any information on adverse treatment effects: two off-label pharmacologic studies[62,63] and one test of an exercise intervention.[64] The most common side effect with exercise was muscle pain.[64] Adverse effects were reported for subgroups in one pooled analysis of duloxetine effects on fibromyalgia patients with major depressive disorder.[44] The treatment-by-MDD interaction for serious adverse events was not significant ($p>0.1$),[44] but the treatment-by-MDD stratum interaction was significant for "treatment-emergent adverse events," with higher rates of 10 adverse effects in treated patients with MDD relative to treated adults without MDD. The three most common of the "treatment-emergent adverse effects" in treated patients were nausea (31.6 percent), headache (19.6 percent), and dry mouth (19.1 percent) in the duloxetine-MDD group, which was 0.4 to 3.3 percent higher than the rates in the treated group without MDD. AEs were reported only by treatment group, not by subgroup, in two pooled milnacipran studies[45,46] and in one duloxetine study.[42] AEs were not reported in the three pooled pregabalin studies.[27,47,48] Only one of four observational studies reported adverse treatment effects in a crossover study of 10 patients treated with naltrexone (off-label).

Strength of Evidence

The strength of evidence for assessing differential treatment effects in subgroups of adults with fibromyalgia is low or insufficient for all types of interventions (pharmacologic, physical, psychological, and mixed). Higher quality studies could change the conclusions of this review. Table B summarizes the major findings and associated strength of evidence for subgroup analyses with at least two studies. All but one comparison, for which we could assign strength of evidence, involved duloxetine effects. Most compared those with and without major depression. All but one duloxetine comparison had low strength of evidence.

For pain, five studies showed no evidence that pain outcomes for adults taking duloxetine differ by depression status.[44,53,55-57] Three studies of duloxetine showed no differences among subgroups on the Patient Global Impression of Improvement (PGI-I) measure.[44,54,55] Two showed no difference on the Fibromyalgia Impact Questionnaire (FIQ) total score with duloxetine.[44,57] Two others with insufficient evidence on duloxetine effects on the Hamilton Rating Scale for Depression did not provide sufficient information to assess the strength of the subgroup outcomes evidence (pooled interaction was not significant[44] and the RCT reported a within-stratum comparison only.[55]

For age, two studies with low strength of evidence found no differences on the BPI average pain severity score[53,55] and another two with low strength of evidence found no differences by age on the PGI-I.[54,55]

The studies of gender differences with low strength of evidence showed a mixed pattern with the BPI average pain severity score; in two there was no difference[53,55] but in one study females improved more than males.[57] When PGI-I was the outcome, in two studies with low strength of evidence there was no treatment effect.[54,55]

Race showed mixed effects in two studies with low strength of evidence; in one there was no difference in BPI average pain severity by race[55] but in the other, non-whites improved more than whites in their BPI average pain severity scores.[53] The same two studies with low strength of evidence showed no difference by race when PGI-I was the outcome.[54,55]

Two studies addressed pain in patients with and without major depressive disorder who received milnacipran but did not report subgroup conclusions. The strength of evidence was insufficient due to outcomes reporting issues: one gave the proportion of 30 percent responders and one had incomplete reporting.

Table B. KQ 1: Benefits of treatment: Summary and strength of evidence of effectiveness and comparative effectiveness of treatments for fibromyalgia in adult subgroups

Population (FM subgroup)	Intervention/ Comparator	Outcome: Change from Baseline	Conclusion	Number of Studies	Strength of Evidence
With major depressive disorder (MDD)/ depression	Duloxetine	Brief Pain Inventory (BPI) average pain severity score	No evidence that treatment effects differ in subgroup	5: 4 RCTs; 1 pooled analysis*	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Patient Global Impression of Improvement (PGI-I)	No evidence that treatment effects differ in subgroup	3: 2 RCTs; 1 pooled analysis*	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Fibromyalgia Impact Questionnaire (FIQ) total score	No evidence that treatment effects differ in subgroup	2: 1 RCT; 1 pooled analysis*	Low (high risk of bias/many study limitations)
	Duloxetine	Hamilton Rating Scale for Depression (HAMD)	Unable to determine (impact of duloxetine on HAMD in adults with MDD and FM)	2: 1 RCT; 1 pooled analysis*	Insufficient (pooled interaction NS; RCT within stratum only)
Age	Duloxetine	BPI average pain severity score	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Sex	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (2 NS; 1 F improved >M)	3 RCTs	Low (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Race	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in	2 RCTs	Low (high risk of bias/many study

Population (FM subgroup)	Intervention/ Comparator	Outcome: Change from Baseline	Conclusion	Number of Studies	Strength of Evidence
			subgroup (1 NS; 1 NW improved >W)		limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
With major depressive disorder/ depression	Milnacipran	Visual Analog Scale (VAS) for pain	Unable to determine (whether milnacipran effects on VAS pain differ in adults with MDD and FM)	2: 1 RCT (NR), 1 post hoc RCT analysis	Insufficient (outcomes reporting issues: 1 indirect, 1 incomplete)

Abbreviations: **F**: female; **FM**: fibromyalgia; **HAMD**: Hamilton Rating Scale for Depression; **M**: male; **MDD**: major depressive disorder; **NR**: not reported; **NS**: not significant; **NW**: nonwhite; **RCT**: randomized clinical trials; **W**: white
*Arnold 2009[44] pooled analysis of patient-level data from 4 RCTs is partially redundant with included RCTs (3 of 4 RCTs included in this report). Rationale for inclusion is provided in the report text

Discussion

Key Findings

Limited, low strength of evidence for subgroup outcomes in adults with fibromyalgia suggests that patient subgroups do not have differential treatment effects compared with other adults with fibromyalgia. Overall treatment effects were small and even less when substantial placebo-group improvements were considered relative to treatment effects. Subgroup effects paralleled the magnitude and direction of overall treatment and placebo effects in mixed-sample studies, and absolute differences between treated and control subgroups were below MCID for the few studies where that could be determined. Reporting of overall interaction results was inconsistent across and within studies, and most interaction results were reported in text only.

We found little evidence to inform treatment decisions for adults with fibromyalgia and complex psychological or medical comorbidities, since individuals with rheumatologic conditions, psychological disorders other than depression or anxiety, and serious medical conditions were uniformly excluded from clinical trials. Little information was reported on individuals over age 55, and extensive medical exclusion criteria likely impacted the participation of older individuals.

The fibromyalgia subgroup outcomes evidence is overwhelmingly pharmaceutical, and the drug trials were based on the most highly selective sampling criteria of all the studies we reviewed. The pharmaceutical industry was heavily involved in study funding, data management and reporting; corresponding authors were commonly employed by industry. Reporting of negative subgroup findings was often difficult to find and was sometimes indeterminable within carefully-selected article text. When reported, data tables most often presented p-values for individual comparisons within strata, rather than the overall negative subgroup interaction results.

In general, sample selection criteria were restrictive, and the extent to which such select patient samples reflect average patients in subgroups of adults with fibromyalgia is unknown. Despite this careful patient selection, attrition by 3-month followup was high (25 to 40 percent in most studies; range 4 percent to 47 percent). Dropouts were typically reported only in aggregate; the effects of attrition on initially small subgroup or even treatment group sample sizes were usually indeterminable.

Adverse effects were reported for subgroups only in one pooled analysis; these did not differ in subgroups. Other common findings were insufficient power for subgroup effects, and lack of correction for multiple outcomes testing.

Applicability and Limitations of the Evidence Base

Several important characteristics limit the generalizability and applicability of these review results.

Study patients were largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ. Sample selection criteria were most restrictive for pharmaceutical studies so that adults with mental health conditions other than depression or anxiety, or those with higher medical comorbidity burden, were excluded. Adults with fibromyalgia and MDD were the most studied subgroup.

Nearly two-thirds of studies that reported subgroup effects were pharmaceutical trials and most assessed the effects of duloxetine. Fewer studies assessed the effects of physical interventions (such as exercise or weight loss), psychological interventions (such as CBT, psychotherapy, or biofeedback), and very few assessed combination treatments.

Most drug trials were placebo-controlled RCTs. Other comparators included standard care, standard care plus adjunctive therapy, normal activities or education and information sessions.

Several issues affect the subgroup outcomes reported in this review. Outcomes are overwhelmingly reported for short-term but not long-term outcomes, the latter of which is of greatest interest in the management of chronic fibromyalgia syndrome. The text on the magnitude of drug treatment effects for specific outcomes rarely acknowledged placebo group improvements that would have minimized the treatment benefits if they had been reported. We noted inconsistencies within and across studies in which subgroup interaction effects were reported, even when methods sections identified that subgroup-treatment interactions were assessed. Selective reporting of subgroup outcomes was most often noted in results tables where individual within stratum comparisons were identified, but the overall interaction term was either not reported or reported only in text. The effect of attrition within subgroups was missing so the extent to which studies could detect a difference, even if one existed, was not determinable, particularly since power calculations, when reported, were conducted to detect main, not subgroup, effects. Finally, although numerous outcomes measures were utilized, limiting aggregating across studies, the range of type of outcomes assessed was not particularly broad. Multiple measures for pain were used. We found that pain, perceptions of global improvement, and changes in the overall impact of fibromyalgia were most commonly reported; physical and social functioning were reported infrequently.

Given this contextual information, the extent to which the fibromyalgia subgroup literature from clinical studies to date reflects the breadth and severity of the broader population of adult subgroups with fibromyalgia is unknown, but complex patients with multiple physical and mental health comorbidities were most often excluded, which limits the applicability of these findings.

Limitations of the Comparative Effectiveness Review Process

The subgroup focus of this review necessitated some modifications to systematic review processes that are used to assess overall benefits and harms of treatments in average adults. In assessing risk of bias, we assessed typical risk of bias domains for RCTs, and added subgroup questions that were supported by the literature, which reflected common sense statistical

practices for subgroup evaluation. We created a quality assessment form for observational studies and added similar subgroup items. We created quality assessment forms for pooled RCT IPD analyses that included quality assessments of the methods and reporting used for the summary analysis and risk of bias assessments of the individual input RCTs. Although risk of bias/study quality assessment is inherently subjective, we tried to evaluate quality as objectively as possible using prespecified forms that were uniformly used and rated by two reviewers.

We did not find evidence on all *a priori* subgroups, such as individuals with higher severity or longer duration of fibromyalgia, or rheumatologic conditions. Fibromyalgia duration and especially baseline severity as assessed with the FIQ were often part of the sample selection criteria for clinical trials, thereby excluding individuals with mild symptoms or impairment and/or shorter syndrome duration. Adults with rheumatologic conditions were routinely excluded.

Research Gaps

Despite the strong belief that the treatment effects for fibromyalgia may vary by subgroup, there is little information about its effect in subgroups. Many of the subgroups identified by experts as clinically important were never investigated or were studied for only a few therapies. Where studies were done, the strength of evidence was low, suggesting that future research might change the conclusions.

Individuals with comorbid mental health conditions other than depression or anxiety, and/or those with higher medical comorbidity burden have been excluded from most clinical trials, especially drug trials. The extent to which such multimorbidity affects treatment needs, feasible treatment options and adverse effects requires further investigation to provide useful treatment information on these clinically complex adults. Individuals with comorbid rheumatologic and other autoimmune disorders are virtually missing from the fibromyalgia treatment outcome s literature, and may require varied treatment approaches to successfully accommodate both conditions.

Despite purportedly high utilization of multicomponent treatments for adults with fibromyalgia, few such studies reported on subgroup effects. Drugs studies dominated in volume of studies that assessed subgroup effects; far fewer studies assessed the effects of nondrug interventions that showed potential benefits.

The vast majority of studies are short term, leaving many questions about the durability of treatment effects in the management of this chronic condition.

Little is reported on functional outcomes in subgroups of patients with fibromyalgia, including physical and social functioning.

Potential differences in subgroup adverse effects warrant greater attention. Although most treatment harms were not serious, potentially differential effects in subgroups were reported in only one pooled IPD RCT analysis.

Transparently-reported, sufficiently powered clinical studies with *a priori* subgroup and hypothesis specifications were lacking, making subgroup treatment effect conclusions tenuous and limited. Efforts to reduce knowledge gaps from research involving fibromyalgia adult subgroups should aim to present findings that are clear and concise for clinicians to interpret.

Conclusions

Limited literature on subgroups of adults with fibromyalgia provides low strength evidence whether or not patient subgroups experience significantly different short-term fibromyalgia treatment effects relative to other adults with fibromyalgia.

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Introduction

Background

Fibromyalgia is a chronic, diffuse musculoskeletal pain syndrome of unknown etiology. It affects mostly adults[1] and is characterized by chronic widespread pain, abnormal processing of and heightened sensitivity to pain, chronic fatigue, sleep disorders, and emotional distress or depression.[1,2] Fibromyalgia reduces quality of life and productivity and is associated with functional disability, lost work time, and increased use of health care services.[1,3-5] Based on diagnostic criteria developed in 1990 by the American College of Rheumatology (ACR), fibromyalgia affects more than 5 million Americans,[6] most of whom are middle-aged women; men are less likely to be diagnosed with fibromyalgia even if they meet diagnostic criteria (3.4 percent women versus 0.5 percent men).[6-8]

Although fibromyalgia can occur in children, diagnosis is typically made in middle age, and prevalence increases with age until age 65, then declines in women.[1,9]

Diagnosis

The diagnostic criteria for fibromyalgia have evolved[10,11] since their first iteration by the ACR in 1990, which included palpation of myofascial "tender points" during physical examination and the presence of widespread pain for at least 3 months.[12] In 2010 the ACR eliminated the tender point examination and added physician-rated severity in two scales, the Widespread Pain Index and the Symptom Severity Scale, and requiring the presence of symptoms for at least 3 months and the absence of another disorder that would account for the symptoms.[10,13] A survey version of the 2010 ACR criteria was also released for research purposes that replaced physician estimates of somatic symptom severity with a patient-generated summary score derived from three self-reported symptom domains.[11] The 2010 ACR preliminary diagnostic criteria compared with those published in 1990 capture a broader population of fibromyalgia patients, which affects prevalence estimates and patient heterogeneity in more recent studies.[13-15]

Because the pathophysiologic mechanism associated with fibromyalgia is unknown, no specific laboratory, imaging, or objective diagnostic test for the syndrome exists.[16] Thus, the diagnostic practices of health care providers for fibromyalgia vary widely in terms of the timing of a fibromyalgia diagnosis relative to other coexisting syndromes with overlapping symptoms.[6,8]

Treatment Strategies

As a syndrome fibromyalgia has no single etiology, and available pharmacological and nonpharmacological modalities help mitigate symptoms and improve function.[1] Current treatments are most often multifaceted and involve multidisciplinary approaches and providers. Treatment goals are to mitigate diffuse musculoskeletal pain, maximize physical and cognitive function, optimize patient self-management and self-efficacy, and manage comorbid medical and psychiatric disorders. Treatment components may include pharmaceutical therapy, exercise programs, cognitive behavioral therapy, patient education (self-management, sleep hygiene, importance of exercise, etc.), and the treatment of comorbid medical and mental health conditions.[1,16] Also common are complementary and alternative medicine (CAM) approaches such as acupuncture, massage, and many others.[16,17] Large-scale fibromyalgia clinics typically use multimodal treatment approaches, although many patients still receive uncoordinated care by seeking treatment from individual health care providers across multiple clinical settings.

Pharmacological Treatments

Pharmacologic interventions include both FDA-approved medications specifically for the treatment of fibromyalgia and other FDA-approved drugs not specifically approved for the management of fibromyalgia symptoms in the United States.

FDA-Approved Drugs for Fibromyalgia

Since 2007, three oral medications have received FDA-approval specifically for the treatment of fibromyalgia: two serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine and milnacipran) and one gamma-aminobutyric acid agonist (pregabalin).

Pregabalin was the first FDA-approved medication for fibromyalgia. Antiepileptic drugs, such as pregabalin, are commonly used to treat neuropathic pain.[18] Although its exact mechanism of action is unknown, pregabalin acts on neurons and results in analgesic, anxiolytic, and antiepileptic effects in animal studies.[18]

Newer SNRIs differ from selective serotonin reuptake inhibitors (SSRIs) because of their reuptake inhibition of both norepinephrine and serotonin neurotransmitters.[19] SNRIs were designed to have superior efficacy in treating depression than SSRIs, and with fewer side effects than tricyclic antidepressants,[18] but the evidence for this is not persuasive.[20] Duloxetine was the first SNRI that demonstrated efficacy for reducing pain in patients with fibromyalgia, although the exact mechanism of action on the perception of pain is unknown. Milnacipran was approved for demonstrating efficacy in concurrent improvements in pain, physical function, and global impression of disease. Additional information on these medications is listed in Table 1.

Table 1. FDA-approved drugs for the treatment of fibromyalgia

Trade Name	Generic Name	Manufacturer	Therapeutic Drug Class	Drug Subclass	Year FDA-Approved
Lyrica	Pregabalin	Pfizer	Antiepileptics	Gamma-aminobutyric acid agonist	2007
Cymbalta	Duloxetine HCL	Eli Lilly and Co	Antidepressants	SNRI	2008
Savella	Milnacipran	Forest Labs/Cypress Bioscience, Inc.	Antidepressants	SNRI	2009

SNRI=serotonin and norepinephrine reuptake inhibitors

Off-Label Use of FDA-Approved Drugs

Numerous pharmacologic agents that have been FDA-approved for other conditions are currently used as primary or adjunctive therapeutics in patients with fibromyalgia ("off-label" usage). Examples include other antidepressants, analgesics, opioid analgesics, anti-inflammatories, and skeletal muscle relaxants and other medications. A table of pharmacologic agents that are used off-label for the treatment of fibromyalgia in the United States is in Appendix A.

Nonpharmacological Treatments for Fibromyalgia

A wide array of nondrug treatments are used to manage pain and other symptoms associated with fibromyalgia, often in combination. Treatment goals are to improve physical function, endurance, and self-efficacy in fibromyalgia management, both short and long-term (Table 2).

Table 2. Nonpharmacological treatments for fibromyalgia

Type	Category	Examples
Psychological	Cognitive behavioral therapy	Cognitive behavioral therapy sessions
	Other cognitive	Mindfulness training
Physical	Passive	Massage therapy, acupuncture, chiropractic; modalities (such as ultrasound, heat, electrical muscle stimulation, etc.); other (such as magnets)
	Active	Supervised or independent exercise (such as aerobic, strength training, stretching, water/pool-based, yoga)
	Multimodal physical	Combinations of Active and/or Passive physical interventions
Multicomponent	Various	Combinations of multiple intervention categories (such as pharmacologic + psychological + physical interventions simultaneously or in coordination)
Lifestyle modifications	Independent or with education, advice or support	Weight loss, dietary changes (such as vegetarian or gluten-free), smoking cessation, sleep habit improvement, etc.
Other therapies	Mind-body therapies	Meditation, hypnosis, tai chi, visualization
	Nutraceuticals	S-adenosyl-methionine (SAMe), coenzyme Q10, omega-3 fatty acids, algae
	Other	Transcranial direct current stimulation

SAMe=S-adenosyl-methionine

Rationale for Review

Many clinical trials suggest a modest benefit from treatments for a general population of fibromyalgia patients.[7,16] Less is known, however, about the efficacy and comparative effectiveness of these treatments for subgroups of adults (defined by number and type of coexisting syndromes or conditions, severity of pain or impairment at baseline,[10] presence of a mood or other mental health disorder, primary complaint at baseline, or demographic or other related factors). For example, moderate to severe depression affects 20 to 40 percent of fibromyalgia patients in clinical trials,[21-24] and approximately 10 percent have anxiety disorders.[25] More information is needed for both patients and providers on treatment outcomes in fibromyalgia subgroups; such patients typically present with complex, chronic symptoms and pose significant treatment dilemmas.

Selection of Patient Subgroups

Certain subgroups of patients have a higher prevalence of fibromyalgia, are more complex or challenging to treat, and/or have historically unsatisfactory treatment outcomes.[6,26] These include:

- Women: Women comprise the majority of fibromyalgia patients and most studies were conducted exclusively in women. More recent studies identified modest differences by sex in clinical features (pain sensitivity, tender point count, depression, sleep disturbance patterns, somatic symptoms, fatigue, and pain duration), modes of treatment, and patterns of health care service use,[27-31] but findings differ by study size. More information is needed about how outcomes differ between men and women for the same modes and intensities of treatment and about which treatment modes best benefit men or women.
- Individuals with coexisting mental health conditions: Coexisting mental health disorders are particularly common in fibromyalgia patients, especially depression and/or anxiety (which occurs in more than one-third of fibromyalgia patients) and substance abuse[1,6,22,32] Traumatic or stressful events and post-traumatic stress disorder may trigger or exacerbate fibromyalgia.[1,33] Simultaneous treatment of co-occurring mental health disorders has been advised, especially in severe cases.[34]

- Individuals with high fibromyalgia symptom severity (Fibromyalgia Impact Questionnaire (FIQ) 59-100):[35] Patients with high FIQ scores report greater functional limitations, higher overall impairment, and more severe symptoms; typical treatments may be less effective[36] or not feasible and may require adaptation to severity.[34,37] These highly-affected individuals present special treatment and management challenges for providers.
- Older adults: More frequent and more severe medical comorbidities in older adults may increase the likelihood of adverse effects, drug interactions, and altered drug tolerance from pharmaceutical therapies for fibromyalgia, increasing the risk for falls, fractures, and other injuries from standard treatments. Recent information shows less impact of fibromyalgia on health-related quality of life (HRQoL) in older women[38] and less fibromyalgia symptomatology in older adults compared with middle-age adults.[39] However, feasible modes of treatment and outcomes may vary in this subgroup.
- Obese adults: Higher rates of obesity and overweight are reported in patients with fibromyalgia, and severe obesity is associated with greater fibromyalgia symptoms and lower quality of life.[40]
- Individuals with multiple medical comorbidities:[41]
  Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS), etc., including osteoarthritis (OA). At least one-third of patients with rheumatic conditions also have fibromyalgia.[1,42]
  Other comorbidities
- Persons with other significant chronic pain conditions:
  Migraine or tension headaches affect more than half of patients.[1,6,22]
  Functional somatic syndromes (e.g., irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint dysfunction, low back pain, and others) are associated with fibromyalgia.[1,16]
  The presence of other functional somatic syndromes with fibromyalgia complicates treatment and compromises outcomes.[43]
- Individuals with longer duration of fibromyalgia symptoms: Longer duration of symptoms is associated with poorer outcomes. Initial assessment values are predictive of longer-term outcomes in fibromyalgia patients seen in rheumatology centers.[41]

Scope and Key Questions

Scope of the Review

This systematic review focuses exclusively on the comparative effectiveness of treatments for fibromyalgia in subgroups of adults who have concomitant conditions or attributes that could potentially require modifications to standard fibromyalgia treatments to improve outcomes.

Unlike most systematic reviews that compare average treatment effects for average patients with a specific condition, the goal of this report is to provide summary information on the evidence to date to support patient and provider treatment choices when comorbid or complex clinical situations are present in adults with fibromyalgia. The subgroups, chosen *a priori,* reflect medically and/or psychologically complex patients or those who reported greater impairment or less responsiveness to treatments. Additional subgroups were included as found in the literature.

We focused our review on treatment effects in subgroups of adults with fibromyalgia because McMaster University in Canada is conducting a comprehensive systematic review of randomized

clinical trials on interventions for fibromyalgia in adults to estimate the relative effectiveness of fibromyalgia treatment approaches.[44] Our systematic review complements the McMaster work by adding unique information on outcomes in fibromyalgia patient subgroups and by including observational literature. Therefore, we focused on addressing whether specific subgroups would benefit from being treated similarly or differently from the general fibromyalgia patient population. We provide brief summary statements of overall (nonsubgroup) study findings only where such results provide necessary context for subgroup treatment effects.

Key Questions

The following two key questions were the focus of this systematic review.

Key Question 1 (KQ 1)

What are the efficacy and comparative effectiveness of treatments for fibromyalgia in specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Persons with multiple medical comorbidities
  Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  Other comorbidities
- Individuals with other significant chronic pain conditions (e.g., low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Key Question 2 (KQ 2)

What are the harms of treatments for fibromyalgia in specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Individuals with multiple medical comorbidities
  Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  Other comorbidities
- Individuals with other significant chronic pain conditions (e.g., low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Components of the PICOTS Framework to answer the key questions on fibromyalgia for this review are described in Table 3.

Table 3. PICOTS framework

PICOTS Element	Inclusion Criteria
Population	Adults (age 18 and older) with fibromyalgia in studies that tested the effectiveness of treatments for fibromyalgia and reported outcomes in at least one of the adult subgroups of interest: sex differences, patients with high symptom severity (e.g., Fibromyalgia Impact Questionnaire (FIQ) scores ≥59 (severe) or severe on a related scale); patients with coexisting mental health disorders; older adults (age 65 or older), obese adults (body mass index (BMI) of 30 or higher or similar),patients with multiple medical comorbidities (rheumatic diseases/osteoarthritis, other), with other chronic pain conditions, or patients with longer duration of fibromyalgia symptoms (such as 1 year or more). Patients met either the 1990[12] or 2010[10] revised fibromyalgia diagnostic criteria from the American College of Rheumatology (ACR), or the Yunus criteria for fibrositis[45] for studies published from 1985-1990. Additional subgroups were included as found in the literature.
Interventions	Pharmacologic treatments that are or were FDA-approved for use in the United States for fibromyalgia or other conditions (off-label use for fibromyalgia) were included. Nonpharmacologic interventions that are or were available for use in the U.S. were included.
Comparators	Placebo, sham, alternate dose or dosing regimen, or any active pharmacologic or nonpharmacologic treatment available for use in the U.S.
Outcomes	**KQ 1**: Change from baseline in any measures used to assess the status in fibromyalgia patients regarding: - Overall pain (such as a Visual Analog Scale [VAS],[46] Brief Pain Inventory,[47] or the McGill Pain Questionnaire,[48] - Symptom improvement (such as the Fibromyalgia Impact Questionnaire [FIQ],[49] Revised FIQ [FIQR],[50] Patient Global Impression of Change [PGI-C],[51] or Patient Global Impression of Improvement [PGI-I][51]) - Physical and/or emotional function (such as the FIQ, FIQR subscales) - Participation in work or social activities (such as the FIQ, FIQR subscales[35,52]) - Health-related quality of life [HRQoL] (such as the SF-36[53]) - Fatigue (such as the Multidimensional Assessment of Fatigue [MAF][54]) - Sleep quality (such as the Medical Outcomes Study [MOS] Sleep Scale[55] **KQ 2**: Adverse effects or harms of intervention(s) - Drug-related side effects (such as dizziness, nausea, fatigue, dry mouth, weight gain, difficulty concentrating, hypertension, thoughts of suicide, peripheral edema, anxiety, tachycardia, constipation, etc.) - Adverse effects from nonpharmaceutical treatments (such as muscle aches, minor injuries or falls during or after exercise; soreness or aches from passive physical treatments such as massage, etc.)
Timing	A minimum of 3 months followup on interventions of any length. Since fibromyalgia is a chronic condition, outcomes improvements over time are more salient to patients and providers than temporary treatment effects.
Setting	Any outpatient setting

Abbreviations: ACR: American College of Rheumatology, BMI=body mass index; FIQ= Fibromyalgia Impact Questionnaire; FIQR=Revised Fibromyalgia Impact Questionnaire; HRQoL=health-related quality of life; MAF=Multidimensional Assessment of Fatigue; MOS=Medical Outcomes Study; PGI-C= Patient Global Impression of Change; PGI-I=Patient Global Impression of Improvement; VAS=Visual Analog Scale

Analytic Framework

The Analytic framework for the Key Questions is depicted in Figure 1.

Figure 1. Analytic framework for treatments for fibromyalgia in adult subgroups

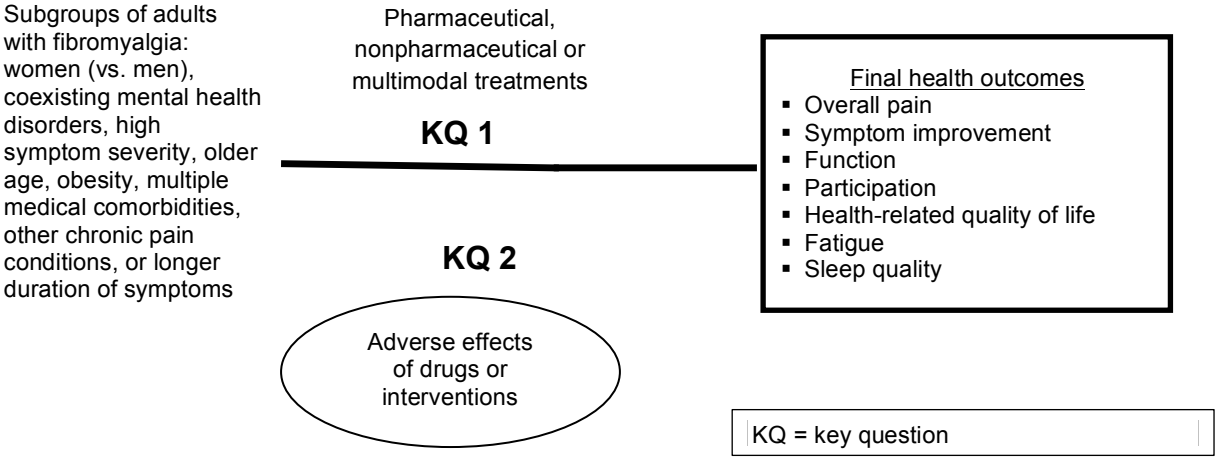


Figure 1 depicts the two key questions within the context of the PICOTS described in Table 3 above. The figure illustrates how the use of pharmaceutical, nonpharmaceutical, or multimodal treatments for fibromyalgia may improve outcomes for adults with fibromyalgia. The patients for this study are subgroups of individuals with fibromyalgia who are identified by at least one of the following characteristics: sex, coexisting mental health disorders, high symptom severity, older age, obesity, multiple medical comorbidities, other chronic pain conditions, or longer duration of fibromyalgia symptoms. The Key Question 1 outcome categories include overall pain, symptom improvement, function, participation (work or social), health-related quality of life (HRQoL), fatigue, and sleep quality. Adverse effects of drugs or interventions may also occur at any point after the treatment (pharmaceutical or nonpharmacuetical) is initiated; these will be examined in Key Question 2.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the ARHQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at http://wwweffectivehealthcare.ahrq.gov/methodsguide.cfm). The main sections in this chapter reflect the elements of the protocol established for this CER; certain methods map to the PRISMA checklist.

Topic Refinement and Review Protocol

The topic of this report and preliminary key questions arose through a public process that involved a topic nomination by a consumer, followed by refinement of the research questions with input from various stakeholder groups including professionals from the disciplines of rheumatology, psychology, psychiatry, physical therapy, nursing, gerontology, chiropractic, and outcomes research. We consulted with these experts to determine which subgroups to address *a priori* in this review.

The draft key questions were posted for public comment on AHRQ's Effective Health Care website from October 25, 2013, through November 14, 2013. Based on that feedback, minor revisions were made to the analytic framework (added symptom improvement as a final outcome, deleted intermediate outcomes as not salient to this topic), and PICOT S (limited treatment to noninpatient settings). We then drafted a protocol for the review and recruited a panel of technical experts to provide high-level content and methodological expertise during the development of the review. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither key informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol which was then refined based on their input, reviewed by AHRQ, and posted for public access on the AHRQ Effective Health Care Website.

Literature Search Strategies

We used bibliographic databases to identify randomized controlled trials, systematic reviews, and observational studies with control groups published from 1985 to the present on treatments for adults with fibromyalgia. Relevant bibliographic databases for this topic included Ovid MEDLINE®, Embase, Ovid PsychINFO, and AMED (Allied and Complementary Medicine) and the Cochrane Central Register of Controlled Trials (CENTRAL).

Our search strategies are included in Appendix B. An experienced librarian in the Minnesota EPC developed the MEDLINE search strategy; we modified the search for other databases. The search strategy used relevant Medical Subject Headings (MeSH®) and natural language terms to identify two fibromyalgia concepts, fibromyalgia, fibrositis and myofascial pain syndrome, and specific filters to identify study designs. We supplemented bibliographic database searches with backward citation searches of highly relevant systematic reviews. The literature searches will be updated while this draft report is under public and peer review.

Inclusion and Exclusion Criteria

Included

Since fibromyalgia is a chronic condition in adults, we limited our analysis to studies of individuals age 18 or older that compared treatments for fibromyalgia in subgroups of adults who were followed 3 months or longer after treatment initiation. We included randomized clinical trials (RCTs), pooled analyses of individual patient-level RCT data, and observational studies that examined one or more treatments for fibromyalgia in adults, utilized a comparator group, and reported treatment outcomes in at least one subgroup 12 or more weeks after the initiation of treatment. RCTs of pure subgroup populations (the study was designed to sample from the subgroup) and those that were not pure subgroups (mixed) were included. We included clinical studies that were published from 1985 to the present in the English language.

Excluded

We excluded studies of drugs or other treatments that were not FDA approved in the United States for any condition. Studies that aggregated patients with different health conditions and did not separately report baseline and outcomes in fibromyalgia patients were excluded. Studies were excluded if they did not use established fibromyalgia diagnostic criteria (American College of Rheumatology [ACR] after 1990 or Yunus[45] criteria for fibrositis from 1985-1990) for subject selection. Studies that did not examine patient-important outcomes (such as brain imaging or lab studies) were excluded. For pharmaceutical trials, we excluded randomized clinical trials where patients were unblinded to treatment for any part of the clinical study or followup, or the blinding status of patients to treatment was unclear or conflicted in the article text.

Study Selection

Two independent investigators reviewed titles and abstracts that resulted from the bibliographic database searches to identify studies that examined interventions for fibromyalgia in adults. Citations deemed as potentially eligible by either investigator underwent full text screening for possible subgroup reporting. Study selection involved an extensive full text review process to identify adult subgroups, since subgroup reporting was commonly not evident in titles and abstracts. Full text articles were initially reviewed to identify outcomes reporting for at least one adult subgroup. A priori subgroups were women, older or obese adults, individuals with coexisting mental health conditions, individuals with high severity or longer fibromyalgia duration, and those with multiple medical comorbidities or other chronic pain conditions. Other subgroups were included as we identified them in the literature. Differences in screening decisions were resolved by consultation between investigators, and when needed, by and a third investigator.

We conducted additional grey literature searches to identify relevant completed and ongoing clinical studies. Grey literature search results were also used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias. We searched ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for studies that specified a fibromyalgia subgroup analysis in their study protocol. We also reviewed Scientific Information Packets sent by manufacturers to AHRQ for recent information on relevant pharmaceuticals and other interventions.

Data Extraction

One investigator trained in research methodology extracted relevant study, population, risk of bias, and outcomes data. Initial data abstraction was quality checked by a second trained investigator. Data fields were determined based upon the proposed summary analysis. These fields included author, year of publication, setting, fibromyalgia diagnostic and severity criteria used, subject inclusion and exclusion criteria, subgroup, intervention(s), allowed and disallowed co-interventions, control characteristics (intervention delivery, timing, frequency, duration), treatment and followup duration, participant baseline demographics, comorbidities, descriptions and results of primary outcomes and adverse effects, results of treatment-by-subgroup interactions, and study funding source. Data were entered into Excel spreadsheets by one trained investigator and checked for accuracy by a second.

Quality (Risk of Bias) Assessment of Individual Studies

The risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design. The two investigators consulted to reconcile any discrepancies in overall risk of bias assessments and, when needed, a third investigator was consulted to reconcile the summary judgment.

For RCTs we assessed the risk of bias using a modified Cochrane Risk of Bias tool.[56] The seven domains of the tool are sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., problems not covered by other domains). To identify potential detection bias, we evaluated outcomes measures for their psychometric properties and assessment methods used to detect change. We also evaluated potential risk-of-bias associated with treatment definition and implementation (treatment fidelity) for nonpharmacologic treatments.

We included additional items to assess the credibility of subgroup analysis of individual RCTs with mixed patient samples based on Sun et al.[57] These guidelines were: if the subgroup variable was measured at baseline, if the subgroup hypothesis was a priori, if the study included only a small number of subgroup hypotheses, if the interaction test suggest a low likelihood of chance explanation, among other contextual issues.[57]

Overall summary risk of bias assessments for each study were classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations[56] Elements contributing to a low risk of bias assessment included whether a study used a random sequence generation, concealed allocation of treatment assignments, blinded outcomes assessors, demonstrated treatment fidelity, had minimal to modest missing outcomes data or balanced missing data across groups with similar reasons for missing data across groups, and credible subgroup analysis methods.[56] High risk of bias elements include nonrandom sequence generation, lack of blinding of outcomes assessors when the outcome was likely to be affected by the lack of blinding, or high and/or differential losses to followup across treatment groups when missing outcomes data may have been related to real outcomes. Moderate risk of bias was be assigned to studies that were challenged across several of the domains but the study was blinded or, if blinding was not possible, outcome assessors were blinded to treatment assignment. The potential for placebo effects in fibromyalgia treatments is high, thus special weight was given to the blinding domain.

We developed an instrument to assess risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank[58] because concerns about selection bias and blinding make the use of observational studies debatable in comparative effectiveness reviews. We selected items most relevant in assessing risk of bias from observational studies of fibromyalgia and to foster consistency with the risk-of-bias instrument for randomized controlled trials[56] Bias issues common to observational studies involve the nonrandom selection of subjects, the completeness and validity of the recording of baseline patient information, attrition, and the ascertainment of outcomes. Items included from the RTI Item Bank address participant selection, group membership, efforts to address selection bias, identification of baseline effect modifiers and confounders, and appropriateness of analytic methods for observational studies. We classified the overall summary risk-of-bias assessments for each individual study as low, moderate, or high based on the collective risk of bias inherent in each outcome domain and confidence that the results are believable given the study's limitations. Similar to risk of bias for RCTs, the overall summary risk of bias was weighted towards low for studies that demonstrated comparability across groups. Moderate risk of bias would have been assigned to large cohort studies with a sample size for adequate power to detect differences, moderate to large effect sizes, and strong evidence of attempting to control for plausible confounders.

We paid special attention to risk of bias assessment for observational studies that pooled patient-level data from randomized clinical trials. Risk of bias of pooled analyses depended in part on the risk of bias of the inputs (RCTs) and the risk of bias in how the pooled analysis was conducted and reported. The risk of bias of the individual RCTs that comprise each pooled analysis was assessed per the Cochrane tool as described above.[56,57] The additional risk of bias in how the pooled analysis was conducted was assessed using the critical appraisal by Fisher et al.[59] of the principal methods for pooling individual-level RCT data to determine treatment-covariate interactions in the literature. Only within-trial patient-level interactions were considered as across-trial information has a higher risk of bias.[59]

The risk of bias assessment forms are included in Appendix C.

Data Synthesis

We summarized the results into evidence tables and qualitatively synthesized evidence by the type of study (RCT, observational, pooled RCT) for each unique population, comparison, and outcome combination within specific followup time periods. Because of the high probability of placebo effects in fibromyalgia treatments, if subgroup analysis was available through an RCT or pooled RCT literature for a given subgroup-treatment-outcome comparison, observational literature with high risk of bias was not included in the analytic set for that comparison Studies were grouped by intervention category and then subgroup.

We synthesized data on several patient-centered outcomes: pain, fatigue, function, and quality of life were the primary outcomes for the review. Pooling was planned for outcomes that assessed the same outcome and had comparable scoring characteristics (such as the FIQ[49] and FIQR[50] tools). When subgroup data was provided, we calculated the absolute difference between treated and control groups by subgroup strata for each outcome and assessed whether or not the difference met or exceeded minimal clinically important differences for fibromyalgia patients (if known). Minimal clinically important differences for fibromyalgia outcomes were obtained from the available literature.

Strength of the Body of Evidence

We evaluated the overall strength of evidence for select clinical outcomes within each comparison based on four domains: (1) study limitations (internal validity); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate) with the study limitations domain having considerable importance.[60] Assessing reporting bias was not required.[58] Study limitations were rated as low, moderate, or high according to study design and conduct. Consistency was rated as consistent, inconsistent, or unknown/not applicable (e.g., single study), based on direction and magnitude of effect. Directness was rated as either direct or indirect based on outcome and study design. Precision was rated as precise or imprecise based on the number of patients needed for an evidence base to be adequately powered. We required the existence of at least two studies (which could be high risk of bias) to assign low rather than insufficient strength of evidence. We required at least one low risk of bias study for moderate strength of evidence and two low risk of bias studies for high strength of evidence. In addition, to be considered moderate or higher, intervention-outcome pairs need a positive response on two out of the three domains other than risk of bias. Based on these factors, the possible SOE grades were:[60]

- **High.** Very confident that the estimate of effect lies close to the true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate.** Moderately confident that the estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable but some doubt.
- **Low.** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient.** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Applicability

Applicability of studies was determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, changes in the diagnostic criteria over time (1990 versus 2010), narrow inclusion criteria or patient and intervention characteristics different than those described by population studies of fibromyalgia treatments. Adults in clinical trials of fibromyalgia treatments may be higher functioning and/or less impaired than the fibromyalgia patient population as a whole to maximize followup. For subgroups, this would not limit applicability but rather limited the number of studies with adequate subgroup inclusion and reporting.

Results

Organization of Results

Results are broadly organized by the Key Questions. The Key Questions are further subdivided by class of treatment (pharmacologic, physical, psychological, or mixed) and within that, by subgroups assessed in the literature, starting with the most frequent subgroups assessed in the literature for that class of interventions.

A complete list of abbreviations and acronyms can be found at the end of this report.

Type and Labeling of Included Studies

This report includes several types of studies. Randomized clinical trials (RCTs) with mixed patient samples refer to those studies that identified a patient subgroup after randomization (such as adults with fibromyalgia, a proportion of whom had depression).

RCTs that selected within particular subgroups (such as sedentary women or postmenopausal women) comprised another group of included studies. We refer to this collection of studies as pure subgroup RCTs.

A third type of study was a pooled analysis of individual patient data from several RCTs to report subgroup outcomes. We refer to these as pooled analyses of individual patient data (IPD) from RCTs, or pooled IPD RCT analyses. All such studies investigated pharmaceutical interventions.

Finally, observational studies with comparator groups were included

Results of Literature Searches

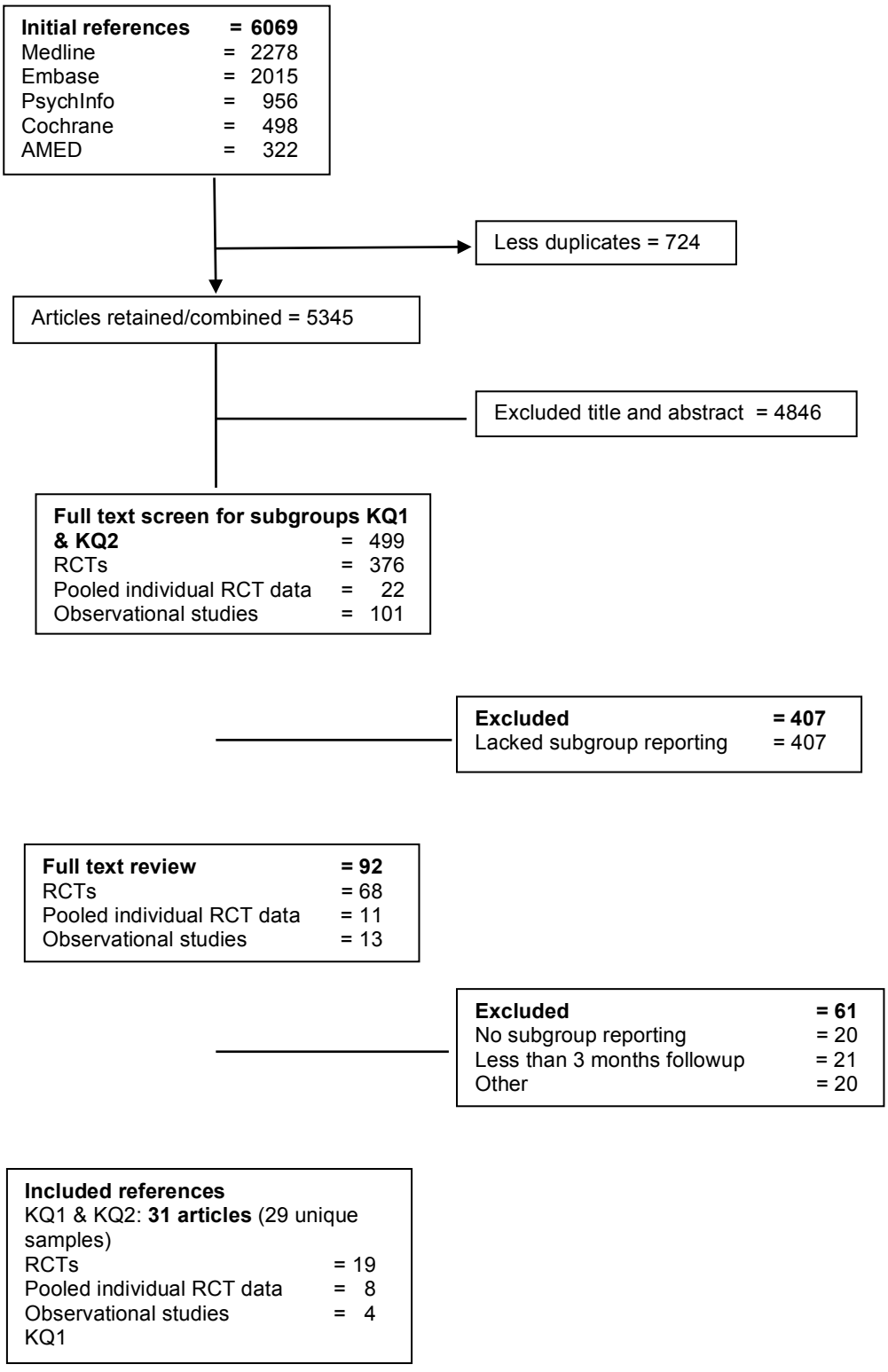
We identified 6069 citations from all databases combined. We examined the full text of 499 articles (376 RCTs, 22 pooled analyses of patient-level RCT data, and 101 observational studies) to assess for subgroup reporting. Of those, 31 studies were included in the analysis (Table 4 and Figure 2): 19 RCTs, eight analyses that pooled IPD from RCTs,[22,61-67] and four observational studies.[68-71] The two types of RCTs included nine studies with mixed patient samples[21,23-25,72-76] and 10 RCTs of pure subgroups.[77-86] Of the 19 RCTs, nine were placebo-controlled trials (seven mixed samples and two pure subgroup studies). Over half of included studies were drug trials (n=19, 61 percent). All included studies were published in 2001 or later, with the eight pooled IPD RCT analyses all published since 2009. Appendix D contains a list of studies that were excluded after the initial full text screen for subgroup reporting, with rationale for exclusion.

Table 4. Included fibromyalgia subgroup studies, by study design

Study Design	Count
Randomized clinical trials	9
Randomized clinical trials of pure subgroups	10
Pooled analyses of individual patient data from randomized clinical trials	8
Observational studies	4
Total of included studies for report	31

Figure 2 shows the QUORUM diagram for the study selection process beginning with the total number of citations retrieved from the literature searches and ending with the number of studies that satisfied the inclusion criteria for this report. Of the 499 references that underwent initial full-text screening, the majority were excluded for lack of subgroup outcomes reporting.

Figure 2. Disposition of fibromyalgia studies identified for this review



Key Question 1. Treatment effectiveness in fibromyalgia subgroups

Overview

Table 5 provides a basic map of the included studies to assess treatment effectiveness in fibromyalgia subgroups. It is readily apparent that little evidence is available for any given treatment-subgroup-outcome combination regarding potential differential treatment effects in subgroups of adults with fibromyalgia. With the exception of studies on Duloxetine, there are few areas where more than one study has examined a treatment-outcome combination for a given subgroup. Persons with depression have been most commonly studied. Five studies looked at pain in this subgroup, all involved treatment with Duluxotine, which we detail below. Pain was the most frequently studied outcome, followed by the measure of Patient Global Impression Improvement.

Sample selection criteria were highly selective, particularly in drug trials. Study specific selection criteria are shown in Appendix Tables E1-E3. Thirty of 31 included studies utilized the 1990 ACR preliminary diagnostic criteria for fibromyalgia; one study did not specify the fibromyalgia diagnostic criteria used (Appendix Tables E1-E3).

Given the sparse evidence for specific treatment-subgroup-outcome combinations, we were unable to conduct meta-analyses. Instead, we present subgroup results in tables in the few instances where data for subgroup outcomes were reported (one RCT[24] and five pooled IPD analyses [61-63,66,68]), provide summary tables of results from articles with text-only reporting of interaction effects, and add qualitative summary information on other comparisons in the text below.

Basic study information for all included studies is provided in Appendix Tables E4-E7.

Key Points

- Limited existing literature on highly affected or clinically complex subgroups of adults with fibromyalgia provides low strength of evidence that patient subgroups do not experience significantly different fibromyalgia treatment effects relative to other adults with fibromyalgia.
- In studies with mixed patient samples, subgroup treatment effects were generally small, beneficial, and paralleled nonsubgroup effects in direction and magnitude.
- Common study issues that bias subgroup study conclusions include very high overall attrition that was often not reported for subgroups or by treatment groups, small subgroup sample sizes, studies not powered to detect subgroup effects and selective reporting of outcomes.
- Adults with fibromyalgia and major depressive disorder were assessed most often, especially the effects of duloxetine on pain. Less information is available on potentially differential treatment effects by age, sex, race, or other subgroups.
- Few studies assessed outcomes beyond 3 months for this chronic condition. The longest trial was 1 year (psychotherapy).
- Outcomes of statistical tests to assess whether treatment effects differ within select subgroups (treatment-by-subgroup interaction results) are most commonly reported in text, or not reported; presentation of data was rare (one RCT), except in pooled IPD RCT analyses.

- Most individual clinical studies were not sufficiently powered to detect differences in treatment effects in subgroups, if they existed

Pharmacological Therapies

The majority of included studies reported the effects of pharmacological therapies on pain and other outcomes in subgroups of adults with fibromyalgia. All eight pooled analyses of patient-level RCT data were pharmaceutical investigations. Duloxetine effects were studied most often (five mixed-sample RCTs[21,23-25,72] and three pooled IPD RCT analyses.[61-63]) Subgroups examined in pharmacologic studies included depression (11 studies), age (five studies), sex (five studies), anxiety (three studies), obesity/Body Mass Index (BMI) (two studies), and medical comorbidities (one study). Additional subgroups found in drug studies aside from our *a priori* listing were race (three studies), baseline fatigue level (one study), postmenopausal women (two studies), and one study that used baseline Visual Analog Scale (VAS) pain ratings for subgroup definition.

The literature set for pharmaceutical interventions is comprised exclusively of high risk of bias studies due to high attrition, lack of attrition reporting for subgroups or treatment groups, and small subgroup sample sizes in nonpooled analyses (Appendix C). Overall attrition in drug trials ranged from 4 percent in one off-label international trial[78] to at least 47 percent,[24] with most studies having high overall attrition (25 to 40 percent). Only two off-label international pharmaceutical trials reported overall attrition of less than 25 percent.[77,78]

At least 16 of 19 drug trials were industry funded among those where funding source was identified (Appendix Tables E4-E7). Industry involvement in studies included data management, statistical support, manuscript drafting, construction of figures and tables, and study management. Corresponding authors in pharmaceutical trials were often industry employees.

Subgroup Outcomes

Comorbid Mental Health Conditions

Depression

Adults with fibromyalgia and major depressive disorder (MDD) or history thereof were the most frequently assessed subgroup for potential differential treatment effects in patients with MDD (treatment interactions) in pharmaceutical studies, and across all other types of treatments. Ten drug studies (seven RCTs, six FDA-approved, one off-label), two pooled IPD RCT analyses and one observational study) assessed treatment-by-MDD interactions on the outcomes of pain, global improvement, fibromyalgia impact, and depression. One additional pooled IPD RCT analysis reported stratum-specific (differences in outcomes in treated versus controls, but only among patients with depression) changes from baseline in a weekly average pain diary rating rather than an interaction effect (Table 6).[66]

We included three RCTs of duloxetine that are contained in one pooled IPD RCT analysis that is also included in this review. One of those three RCTs reported subgroup data at 3- and 6-months for the BPI average pain score and PGI-I for adults with and without MDD.[24] We show the 6-month subgroup data in Table 7.[24] The other two overlapping RCTs provided text-only summary statements about interaction effects on the BPI average pain score.[23,72] For the pooled IPD analysis by Arnold et al. 2009[63] the 3-month pooled results on BPI average pain for adults with and without MDD are shown in Table 8. We included both the three (of four) input RCTs

for the pooled IPD analysis and the individual RCTs to qualitatively assess the consistency of treatment effects with a larger subgroup sample.

Pharmacologic treatments did not appear to have differential effects in adults with both fibromyalgia and depression compared to those with fibromyalgia but without depression. Pain was the most common outcome assessed in adults with fibromyalgia and comorbid depression, including five RCTs (four of duloxetine[21,23,24,72] and one of milnacipran,[73]) and two pooled RCT analyses,[62,63] both of duloxetine. All treatment-by-MDD interactions on pain as an outcome in the pharmacologic studies we examined were either not significant or not reported. Five different measures were used to assess pain in the MDD subgroup, with the BPI average pain severity score being utilized most often (Appendix Tables E8 and E9). For pain, one high risk of bias RCT by Russell et al.[24] and one pooled IPD RCT analysis of four high risk of bias RCTs[63] of duloxetine trials presented data on MDD subgroup outcomes for the BPI average pain severity score (Tables 7 and 8). Although MDD subgroup data were presented, the RCT by Russell et al. did not explicitly report the interaction result; the text implies that it was not significant.[24] The differences between treated and control patients with or without MDD did not exceed minimal clinically important differences in either study, as determined for adults with fibromyalgia.[87]

The RCT by Russell et al. 2008[24] also displayed MDD subgroup data for the Patient Global Impression of Improvement (PGI-I), a 7 point scale ranging from 1 (very much better) to 7 (very much worse).[51] Study authors noted similar improvements in PGI-I in treated versus controls regardless of MDD status. However, dropouts were assigned a PGI-I score of 4 (corresponding to no change) for the analysis, which assumed no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases[24] (Table 7).

All other treatment-by-MDD interaction results were reported in article text only, with or without p-values. All treatment-by-MDD interactions were not significant or not specifically reported (Tables 9 and 10).

The FIQ and FIQ pain subscales were examined as primary outcomes in two RCTs, one of duloxetine[72] and one of fluoxetine.[74] Both treatment-by-MDD interactions on the FIQ pain subscales[72,74] and FIQ total scores[72] were not significant.

For the Patient Global impression of Improvement (PGI-I) outcome, the duloxetine-by-MDD interaction in two RCTs was not statistically significant[25] or not reported.[24]

The high risk of bias duloxetine RCT by Russell et al. also assessed changes between treated and placebo-controlled patients on the Hamilton Depression Rating scale but within the MDD stratum.[24] Within the major depressive disorder subgroup, changes in the Hamilton Depression Scale from baseline to 6 months in treated versus controls were not significantly different (Table 11).

One observational study of milnacipran was a post-hoc analysis of RCT data that stratified by baseline Beck Depression Inventory score to assess improvement in VAS pain scores. No formal statistical analysis was conducted for subgroup effects.[68]

These reported results should be considered along with issues common to this set of studies. At baseline, MDD subgroup sample sizes were small in all RCTs, excluding the pooled IPD RCT analyses. The number of patients with MDD at final followup in both treatment and control groups were usually not determinable due to incomplete reporting of denominator values and dropouts per subgroup or by treatment groups after baseline. The lack of denominator values after baseline was common in both RCT and pooled analyses.

The collective strength of evidence for the beneficial effects of duloxetine on pain (BPI average pain score), global improvement (PGI-I) and impact of fibromyalgia (FIQ total score) was low for all three outcomes (Table 12).

Anxiety

The interaction of duloxetine treatment and generalized anxiety disorder (GAD) on the outcomes of BPI average pain and global improvement (PGI-I) were considered in two RCTs[21,25] for a total of 63 GAD-affected patients. Both interaction terms were not significant. One additional pooled IPD RCT analysis of pregabalin reported stratum-specific changes from baseline in a weekly average pain diary rating rather than an interaction effect for persons with fibromyalgia and anxiety[66] (Table 6).

Age

Five pharmaceutical studies examined potential age-related differences in treatment effectiveness in adults with fibromyalgia: three high risk of bias RCTs[21,24,25] and two pooled analyses of IPD from high risk of bias RCTs.[61,67]. Four of five studies tested duloxetine effects (three RCTs[21,24,25] plus one pooled IPD RCT analysis[61]) and one pooled IPD analysis examined (pregabalin).[67] All investigations reported 3-month outcomes; only one mixed sample RCT also assessed outcomes at 6 months[24] after treatment initiation. Treatment-by-age interactions were not significant for pain (Brief Pain Inventory [BPI] average pain severity), global improvement (PGI-I) or on the Fibromyalgia Impact Questionnaire (FIQ) stiffness subscale. The pooled IPD analysis by Bennett et al.[61] provided pooled data for nonsignificant differences in the effect of duloxetine on dichotomized age (summarized in Table 8) The pregabalin article was a statistical modeling paper that provided summary comments of effect only and reported greater pain reduction in older versus younger patients.[67]

Sex

Seven pharmacologic studies reported subgroup outcomes by sex. Five studies examined sex as a treatment effect modifier: four high risk of bias RCTs[21,24,25,72] plus one pooled IPD RCT analysis.[67] All five studies assessed the effects of duloxetine. Followup was 3 months in all studies; one RCT also assessed outcomes at 6 months.(Russell 2008 #167) Three of four RCTs reported that treatment-by-sex interactions were not significant for BPI average pain and Patient Global Improvement (PGI-I). Only one high risk of bias RCT (Arnold 2004[72]) found significant treatment-by-sex interactions on nonprimary outcomes, with statistically significant improvement in pain (BPI average pain) ($p=0.046$) and the Sheehan Disability Scale ($p=0.007$) in women verses men. The pooled analysis/statistical modeling paper of four RCTs with 8-14 weeks of followup reported greater pain reduction in females versus males in text but did not provide useable interaction results.[67]

Two additional pure subgroup RCTs assessed pharmacologic effects in patient samples that were limited to postmenopausal women. Both had a high risk of bias. One underpowered study examined the effects of transdermal estrogen versus placebo on pain and found no difference between groups.[77] The second study of 100 women found that raloxifen-treated women had greater mean reduction in pain, sleep disturbance, and tender points but no effect on anxiety and depression relative to placebo-treated women.[78]

Race

Although not listed as an *a priori* subgroup due to the expected small number of nonwhite race patients in fibromyalgia trials, treatment-by-race interactions were assessed in three RCTs, all of duloxetine. The outcomes included BPI average pain severity[21] and global improvement (PGI-I).[24,25] The interaction was not significant in two of three RCTs. However, Arnold et al. 2012[21] reported a significantly greater mean decrease (improvement) in BPI average pain in non-White (versus White) patients taking duloxetine 30mg/day. We note that the sample size for the nonwhite subgroup was small at baseline (22 treated, 17 placebo) and was not reported for the 3 month followup.

Obesity

Two pooled IPD analyses examined the outcomes of stiffness (FIQ subscale) and weight loss for subgroups determined by BMI at baseline: one of duloxetine and one of milnacipran. All input RCTs for these pooled IPD analyses were high risk of bias studies. The duloxetine pooled IPD analysis[61] assessed whether treatment effects on stiffness associated with fibromyalgia, measured by the FIQ stiffness subscale (one item), varied by BMI. The 3-month outcomes data were reported, stratified by BMI (normal, overweight, obese, and morbidly obese) (Table 8). The treatment-by-BMI interaction effect of duloxetine on changes in the FIQ stiffness measure was not significant. However, the small differences between treated and placebo-controlled patients in changes in FIQ stiffness from baseline decreased with increasing levels of BMI; only baseline enrollment numbers were reported and no power calculation was provided for the subgroup comparison. None of the differences between treated versus placebo within BMI strata met MCID (13 percent change) for the FIQ stiffness subscale (Table 8).[35]

Fatigue

Bradley et al.[62] conducted a pooled analysis of IPD RCT data to determine whether the effects of duloxetine on the BPI average pain score varied by baseline level of fatigue as measured by the FIQ tiredness subscale. Subgroup data were presented and can be reviewed in Table 8. The interaction term was not significant ($p>0.1$). Differences between treated and control subjects in the change in BPI average pain within tiredness strata did not meet MCID.

Other Subgroup Outcomes

Within-subgroup changes from baseline in pain were reported by Bhadra et al.[66] in a study of varying doses of pregabalin, although no interaction effects were assessed (Table 6). No other subgroups were separately reported in included studies.

Strength of Pharmaceutical Evidence

The strength of evidence was low for the effectiveness of all pharmaceutical interventions in alleviating symptoms of fibromyalgia syndrome. Individual clinical trials all had high risk of bias (Appendix Tables E10-E12).

Physical Treatments

Due to the sparse literature on physical treatment effects in subgroups of adults with fibromyalgia, this section is organized by the type of study design, and subsequently, by specific type of intervention. All physical interventions were assessed in pure subgroup RCTs. Study duration ranged from 3 months to 6 months (Appendix Table E5).

Five pure subgroup RCTs examined the effects of physical interventions[79-81,83] or dietary changes[82] on outcomes in subgroups of adults with fibromyalgia. Three of five RCTs examined exercise interventions.[79,81,83] Two studies of physical interventions had moderate risk of bias;[79,80] all others were high risk of bias. Sample sizes ranged from 21 to 83 adults at enrollment, for a total of 231 subjects across all five studies.

One moderate risk of bias RCT exclusively of sedentary women with fibromyalgia[79] compared the aerobic exercise interventions of deep water running versus land-based exercise (control) on the outcomes of fibromyalgia impact (FIQ), pain (VAS), depression (BDI), health status (SF-36), and Patients Global Assessment of response to treatment (PGART). Both groups improved significantly with 15 weeks of three times per week exercise, with greater improvements in the FIQ in the deep water running group. There were no differences in improvement from baseline between groups in all other measures.

Gusi et al.[80] assessed the effects of whole body vibration on dynamic balance in a post hoc analysis of RCT data by baseline body weight. This moderate risk of bias studies found that participants with the heaviest weight and worst balance at baseline improved more than others ($p<0.001$).

Two exercise interventions were evaluated in females with fibromyalgia based on their menopausal status;[81,83] both studies had a high risk of bias. Hakkinen et al.[81] evaluated the isometric knee strength and serum hormone effects of 21 weeks of supervised strength training in premenopausal women. Only isometric knee strength increased significantly in the strength-trained versus normal activities group. The high risk of bias Valkeinen study[83] of strength and aerobic training versus no training in postmenopausal women age 50 and older reported a 2 percent improvement in strength and significant improvements in pain, walking, and stair climbing ability in the trained versus no strength or aerobic training group, with no differences in fatigue, well-being, or sleep quality reported.

The strength of evidence was insufficient to compare treatment outcomes by physical interventions in these pure subgroup RCTs. All studies tested unique treatments in unique subgroups and had small sample sizes; three of five were high risk of bias studies. (Appendix Table E10).

Psychological Therapies

Only four studies examined the effects of psychological therapies in subgroups of adults with fibromyalgia: one mixed-sample RCT,[75] two pure subgroup RCTs,[84,85] and one observational study.[70] Study duration ranged from 3 months to 1 year, which was the longest followup of any studies included in this report. Sample sizes were small; the total number of adults included across these psychological studies was 210. All assessed unique outcomes in disparate subgroups and all were high risk of bias studies.

Junghaenel et al.[75] compared outcomes in fibromyalgia patients by their level of education and dominant pain coping strategy at baseline to assess the effects of a written emotional disclosure intervention on pain, fatigue, and psychological wellbeing in a mixed-sample RCT. Outcomes from the writing intervention did not differ by level of education or baseline pain coping strategy for pain or fatigue, but adults with the pain coping strategy called "interpersonally-distressed" improved more in the psychological wellbeing outcome than did the "adaptive" pain coping group. Also, only graduate-educated adults had significant improvements in psychological well-being with the intervention compared to less educated individuals.

The longest of all included studies was a year-long study of the effects of psychotherapy versus four primary care consultations with advice on medication and exercise on multiple outcomes. This high risk of bias pure subgroup RCT included women with fibromyalgia, all of whom had concomitant psychological comorbidity, including MDD, dysthymia, anxiety, and double depression.[85] Both interventions were deemed to be equally effective; there were no significant outcomes differences from psychotherapy versus primary care interventions by type of baseline psychological comorbidity. This was the only study that included patients with mental health conditions other than major depressive disorder or anxiety.

One high risk of bias pure subgroup RCT compared CBT versus other behavioral therapy versus usual care on sleep patterns in adults with fibromyalgia and insomnia. Both treatment groups improved, with the CBT group showing the greatest improvements in polysomnography assessed wake times.

One high risk of bias observational biofeedback study examined the benefits of using EMG-reduction training of visual and auditory feedback to teach subjects muscle relaxation techniques.[70] Subjects were stratified by baseline Minnesota Multiphasic Personality Inventory (MMPI) scores to assess outcomes of pain perception, tender point scores, and the SF-36. Although the group with "psychologically abnormal" MMPI scores was worse off than "psychologically normal" women in all measures at baseline, the *psychologically abnormal* group had improvements in all outcomes measures, including pain and fibromyalgia symptoms, which were not experienced in the comparator group of women.

The strength of evidence was insufficient to compare subgroup treatment effects for psychological interventions in these four studies due to their high risk of bias and small sample sizes (Appendix Table E10 and E11).

Mixed Types of Treatments

Three studies assessed combination therapies, and each study had a high risk of bias. A mixed sample RCT included a subgroup of 16 patients with fatigue.[76] Multidisciplinary treatment with CBT showed greater improvements in the FIQ total score and SF-36 emotional well-being in fatigue patients than with multidisciplinary treatment alone. The study was not powered to assess subgroup effects.

Fontaine et al.[86] assessed the effects of a cognitive behavioral physical activity promotion program on multiple outcomes in adults with fibromyalgia who had suboptimal physical activity in the prior 6 months per U.S. Surgeon General's recommendations. The treated group increased daily walking (count of steps) by 54 percent, and had a significant reduction in mean total FIQ (-16 percent; MCID is 14 percent[35]) and reduction in the FIQ pain subscore. No differences were noted in the 6 minute walk test, BMI, fatigue, depression, or number of tender points between groups.

One observational study evaluated the effects of supervised multifaceted exercise and relaxation (exercise plus relaxation) versus amitriptyline for subgroups determined by socioeconomic status and FIQ pain score.[71] Both strategies equally reduced disability.

The strength of evidence was insufficient to compare treatment outcomes for mixed types of fibromyalgia treatments. All three studies assessed unique treatment-subgroup-outcomes combinations, and all had a high risk of bias (Appendix Tables E10 and E11).

Placebo groups in pharmacologic RCTs often showed considerable improvements, but the improvement was generally not discussed when the magnitude of treatment effects were reported.

Key Question 2. Adverse treatment effects in fibromyalgia subgroups

The clinical trial literature on adults with fibromyalgia that reported on subgroup treatment effects was nearly devoid of adverse effect (harms) reporting for subgroups. Therefore, this section is organized by the type of study design, under which we report summary information on harms only.

Key Points

- Harms were rarely reported by subgroup.
- There was insufficient evidence to determine whether or not adverse effect of treatments for adults with fibromyalgia vary in adult subgroups or whether subgroups experience atypical harms for a given treatment.
- When reported, adverse effects did not markedly differ in subgroups.

RCTs

None of the nine mixed sample RCTs with subgroup outcomes separately reported adverse effects (AEs) by subgroups.[21,23-25,72-76]

Pure Subgroup RCTs

Of the ten RCTs that sampled within at least one subgroup, only three reported any information on adverse treatment effects: two off-label pharmacologic studies[77,78] and one test of an exercise intervention.[79] The most common side effect in the deep water running versus land-based exercise intervention was muscle pain, which was more common in the land-based exercise control group.[79] The raloxifen versus placebo study[78] reported one serious AE (deep vein thrombosis, 2 percent of treated group) with less severe issues of leg cramps, anxiety, and flushing affecting 10-15 percent of the treated group. The second small RCT tested transdermal 17B-estradiol on pain in 29 women.[77] The study was halted at half the planned sample size due to new information that emerged with concerns for the health effects of hormone replacement therapy.

Pooled IPD RCT Analyses

Adverse effects were reported for subgroups in one pooled analysis of duloxetine clinical trials.[63] In a pooled analysis of patients with fibromyalgia and major depressive disorder, the treatment-by-MDD interaction for serious adverse events was not significant ($p>0.1$).[63] However, the treatment-by-MDD stratum interaction was significant for "treatment-emergent adverse events," with higher rates of 10 adverse effects in treated patients with MDD relative to treated adults without MDD. The three most common of the "treatment-emergent adverse effects" in treated patients were nausea (31.6 percent), headache (19.6 percent) and dry mouth (19.1 percent) in the duloxetine-MDD group, which was 0.4-3.3 percent higher than the rates in the treated group without MDD. The lower proportion of placebo-treated patients with MDD that experienced these adverse effects was similar to those experienced by placebo-treated adults without MDD.

AEs were reported only by treatment group, not by subgroup, in two pooled milnacipran studies[64,65] and in one duloxetine study.[61] AEs were not reported in the three pooled pregabalin studies.[22,66,67]

Observational Studies

Only one of four observational studies reported adverse treatment effects in a crossover study of 10 patients treated with naltrexone (off-label) versus placebo that were grouped by baseline erythrocyte sedimentation rate (ESR). The most common AEs were vivid dreams, nausea, and insomnia.

Table 5. Number of studies that assessed various subgroup-treatment-outcome combinations in adults with fibromyalgia

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Drugs									
Duloxetine									
Depression/MDD	5 Arnold, 2012[21] Russell, 2008[24] Arnold 2005[23] Arnold 2004[72] Arnold 2009[63]*	3 Arnold, 2010[25] Russell, 2008[24] Arnold, 2009[63]*	2 Arnold, 2004[72] Arnold, 2009[63]*	1 (pain) Arnold, 2004[72]			2 Russell, 2008[24] (within strata) Arnold, 2009[63]		1 each outcome: SF-36 Arnold, 2009[63]; SDS, CGI-S, MFI; Arnold, 2009[63]
Anxiety/GAD	1 Arnold, 2012[21]	1 Arnold, 2010[25]							
Age	2 Arnold, 2012[21] Russell, 2008[24] Arnold, 2004[72]	2 Arnold, 2010[25] Russell, 2008[24]		1 (stiffness) Bennett, 2012[61]		1 (NR) Byon, 2010[67]		1 (NR) Byon, 2010[67]	
Sex	3 Arnold, 2012[21] Russell, 2008[24] Arnold, 2004[72]	2 Arnold, 2010[25] Russell, 2008[24]	1 Arnold, 2004[72]	1 (pain) Arnold, 2004[72]		1 (NR) Byon, 2010[67]		1 (NR) Byon, 2010[67]	1:SDS Arnold, 2004[72]
Race	2 Arnold, 2012[21] Russell, 2008[24]	2 Arnold, 2010[25] Russell, 2008}[24]							
Obesity/BMI				1 (stiffness) Bennett, 2012[61]					
Fatigue/Tiredness	1 Bradley, 2010[62]	1 Bradley, 2010[62]	1 Bradley, 2010[62]	1 (multiple) Bradley, 2010[62]					1 (SF-36) Bradley, 2010[62]
Milnacipran									
Depression					2 Gendreau, 2005[73] Arnold,	1 Arnold, 2012[68]		1 (3 different pain scores)	1 (Beck Depression) Arnold, 2012[68]

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
					2012[68]			Gendreau, 2005[73]	
Obesity/BMI									1 (weight loss) Arnold, 2012[64]
Baseline VAS pain					1 Geisser, 2011[65]	1 Geisser, 2011[65]			1 (SF-36 PCS) Geisser, 2011[65]
Pregabalin									
Depression						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	1 (HADS-D) Arnold, 2010[22]
Anxiety						1 (within stratum) Bhadra. 2010[66]		1 (within stratum) Bhadra, 2010[66]	1 (HADS-A) Arnold, 2010[22]
Immune/allergies						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
GI reflux						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
Insomnia						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
IBS						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
Neurological						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
Asthma						1 (within		1 (within	

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
						stratum) Bhadra, 2010[66]		stratum) Bhadra, 2010[66]	
Restless legs/RLS						1 (within stratum) Bhadra, 2010[66]		1 (within stratum) Bhadra, 2010[66]	
Off-label									
Depression (Fluoxetine)			1 Arnold, 2002[74]	1 (pain) Arnold, 2002[74]					
Postmenopausal women (17B-estradiol)								1 Stening, 2011[77]	
Postmenopausal women (Raloxifen)								1 Sadreddini, 2008[78]	1 (4 other measures) Sadreddini, 2008[78]
ESR level at baseline (Naltrexone)									1 (FM symptom severity) Younger, 2009[69]
Physical									
Sedentary women (deep water vs land based exercise)			1 Assis, 2006[79]		1 Assis, 2006[79]				1 (BDI, SF-36, PGART) Assis, 2006[79]
Body weight (whole body vibration)									1 (dynamic balance) Gusi, 2010[80]
Premenopausal women(strength training)									1 (knee strength, hormones) Hakkinen, 2001[88]
Obese adults(weight reduction)			1 Senna, 2012[82]						1 (BDI, Sleep quality index, TPs) Senna,

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
									2012[82]
Postmenopausal (strength and aerobic training)									1 (5 measures) Valkeinen, 2008[83]
Psychological									
Baseline MMPI (EMG-biofeedback)								1 Drexler, 2002[70]	1 (SF-36 and 3 other measures) Drexler, 2002[70]
Insomnia (CBT)									1 (polysomnography) Edinger, 2005[84]
Women –all with psychological comorbidity (psychotherapy)			1 Scheidt, 2013[85]					1 Scheidt, 2013[85]	1 (2 other measures) Scjeidt, 2013[85]
Coping style (Written emotional disclosure)								1 Junghaenel, 2008[75]	1 (fatigue, psychological well-being) Junghaenel, 2008[75]
Educational status (Written emotional disclosure)								1 Junghaenel, 2008[75]	1 (fatigue, psychological well-being) Junghaenel, 2008[75]
Mixed									
Fatigue (Multidisciplinary plus CBT or medications)			1 Lera, 2009[76]						1 (SF-36, SCL-90-R) Lera, 2009[76]
Sedentary adults (cognitive-behavioral physical activity promotion program vs. information)			1 Fontaine, 2010[86]	1 Fontaine, 2010[86]	1 Fontaine, 2010[86]				1 (4 other measures) Fontaine, 2010[86]

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Severe fibromyalgia (exercise and relaxation vs. drug)			1 Joshi, 2009[71]						
Socioeconomic status (exercise and relaxation vs. drug)			1 Joshi, 2009[71]						

Abbreviations: **BDI**: Beck Depression Inventory; **BMI**: Body Mass Index; **BPI**-Brief Pain Inventory; **CBT**-Cognitive Behavioral Therapy; **CGI-S**-Clinical Global Impression of Severity Scale; **EMG**: Electromyography; **EQ-5D**- EuroQol health outcomes assessment; **FIQ**-Fibromyalgia Impact Questionnaire; **GAD**-Generalized Anxiety Disorder; **GI**: gastrointestinal; **HADS-A**-Hospital Anxiety and Depression Scale, anxiety subscale score; **HADS-D**-Hospital Anxiety and Depression Scale, depression subscale score; **HAMD**-Hamilton Rating Scale for Depression; **IBS**: Irritable Bowel Syndrome; **MDD**-Major Depressive Disorder; **MFI**-Multidimensional Fatigue Inventory; **NR**: not reported; **PGART**-Patient Global Assessment of Response to Therapy; **PGI-C**-Patient Global Impression of Change Scale; **PGI-I**-Patient Global Impression of Improvement Scale; **RLS**: restless legs syndrome; **SDS**-Sheehan Disability Scale; **SCL-90-R** - Symptom Checklist-90-Revised; **SF-36**-MOS Short-Form 36-item Health Survey; **SF-36 PCS**: SF-36 Physical component score; **TPs**-Tender Points; **VAS**-Visual Analog Scale

*Arnold 2009[63] pooled analysis of patient-level data from 4 RCTs is partially redundant with included RCTs (3 of 4 RCTs included in this report. Rationale for inclusion is provided in the report text

Table 6. Pregabalin results from pooled patient-level RCT study: mean change from baseline in Weekly Mean Pain Diary Score (11 point scale) by comorbid condition

Author, Year	Followup duration	Comorbid Condition at Baseline*	Placebo	Pregabalin 300 mg/day	Pregabalin 450 mg/day	Pregabalin 600 mg/day
Bhadra, 2010[66]	8-12 weeks	Headache	-1.0	-1.7	-1.7	-1.5
		Immune/allergies	-1.1	-1.8	-1.9	-2.0
		GI reflux	-1.1	-1.9	-1.9	-1.8
		Insomnia	-1.3	-2.0	-2.0	-2.0
		Depression	-1.0	-1.6	-1.9	-2.1
		IBS	-1.1	-1.6	-2.1	-1.7
		Neurological	-1.1	-2.0	-1.9	-1.9
		Asthma	-1.0	-2.1	-1.9	-2.1
		Anxiety	-1.1	-1.8	-1.4	-2.0
		RLS	-1.6	-1.6	-1.7	-2.0

Abbreviations: **GI**-gastrointestinal; **IBS-**irritable bowel syndrome; **RLS**-restless legs syndrome

* Comorbid conditions not mutually exclusive

Table 7. Duloxetine randomized clinical trial with subgroup data showing 6 month outcomes in adults with fibromyalgia, with or without major depressive disorder

Author, Year Time	Outcome Measure	Subgroup	N-tx	Dose, Mean BPI Change from Start	N-c	Placebo N=144	Difference (tx-c)*	Interaction p value
Russell, 2008[24] 6 months	Brief Pain Inventory (BPI) average pain severity**	Major depressive disorder (MDD) (24% of patients)	**79**[a]	**20 mg/day**‡				NR
		With MDD	22	-2.58 (0.53)	35	-1.35 (0.45)	-1.23	
		Without MDD	57*	-2.16 (0.34)	109*	-1.48 (0.25)	-0.68	
			150[a]	**60 mg/day**				
		With MDD	35	-2.35 (0.46)	35	-1.35 (0.45)	-1.00	
		Without MDD	115*	-1.93 (0.25)	109*	-1.48 (0.25)	-0.45	
			147[a]	**120 mg/day**				
		With MDD	34	-2.56 (0.48)	35	-1.35 (0.45)	-1.21	
		Without MDD	113*	-2.20 (0.25)	109*	-1.48 (0.25)	-0.72	
				Dose, PGI-I score				
	Patient Global Impression of Improvement (PGI-I)***		**79**[a]	**20 mg/day**‡				*Similar improvements in PGI-I in treated vs. controls regardless of MDD status*
		With MDD	22	2.85 (0.33)		3.28 (0.28)	-0.43	
		Without MDD	57*	2.76 (0.22)		3.37 (0.16)	-0.61	
			150[a]	**60 mg/day**				
		With MDD	35	2.96 (0.29)		3.28 (0.28)	-0.32	
		Without MDD	115*	3.07 (0.16)		3.37 (0.16)	-0.30	
			147[a]	**120 mg/d**				
		With MDD	34	2.41 (0.30)		3.28 (0.28)	-0.87	
		Without MDD	113*	3.04 (0.16)		3.37 (0.16)	-0.33	

Abbreviations: **BPI**-Brief Pain inventory; **MDD**: major depressive disorder; **N-tx**: number in treatment group; **N-c**: number in control group; **PGI-I**-patient global impression of improvement scale; **(tx-c)*-**difference in mean outcome between treated and control groups (treated minus control)

BPI: Treatment by subgroup interactions not significant for age, sex and race at 3 or 6 months (p-values reported but no data).
a: Denominators for both 3 and 6 month followup in Table 2 of the article report baseline enrollment totals by treatment group that do not reflect dropouts.
Of the 520 randomized patients, 325 (62.5%*) completed the study for 3 months, and 278 for 6 months. Denominators for the number of patients per dose at 3 and 6 month followups were not reported in tables or text.
‡: Duloxetine patients on the 20mg dose during the first 3 months had their dose blindly increased to 60 mg/day for months 4 through 6 (n=49 [a]).
* Calculated by the MN EPC, not article authors
** Minimum clinically important difference (MCID) for the BPI average pain severity score in fibromyalgia patients is 2.1 points[87]
***PGI-I: 7 point scale ranging from 1 (very much better) to 7 (very much worse). Dropouts were assigned a PGI-I score of 4 (corresponding to no change); the analyses assume no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases.[24]

Table 8. Results from pooled patient-level RCT data: primary outcome with subgroup changes from baseline in pooled studies that reported subgroup data

Drug **Author, Year**											
Duloxetine	**Time**	**Outcome**	**Subgroup**	**N-tx** Base-line	**Treatment, Dose**	**N-c** Base-line	**Control**	**Difference (tx-c)***	**Interaction p value**	**Difference > MCID?**	**MCID Reference**
Bennett, 2012[61]	3 months	FIQ stiffness change (0-10 scale)	**Age** (years)		**Duloxetine 60 and 120 mg/day**		**Placebo**		0.246		13% change in FIQ stiffness[35]
			<55	485	-2.43(0.12)	345	-1.50 (0.12)	-0.93		no	
			≥55	275	-2.14(0.17)	172	-1.50 (0.12)	-0.67		no	
			BMI						0.102		
			Normal	208	-2.40(0.18)	157	-1.36 (0.21)	-1.04		no	
			Overweight	230	-2.08(0.17)	149	-1.31 (0.21)	-0.77		no	
			Obese	253	-2.51(0.17)	164	-1.80 (0.20)	-0.71		no	
			Extreme obesity	62	-2.01(0.34)	41	-1.53 (0.41)	-0.48		no	
Bradley, 2010[62]	3 months	BPI average pain score	**FIQ Tiredness**		**Duloxetine 60 and 120 mg/day**				>0.1		2.1 points for BPI average pain[87]
			mild	9**	-1.3(0.5)	20	-1.8 (0.5)	+0.5		no	
			moderate	50**	-1.6(0.2)	83	-1.1 (0.2)	-0.5		no	
			severe	204**	-2.0(0.1)	430	-1.1 (0.1)	-0.9		no	
Arnold, 2009[63]	3 months	BPI average pain score	**Major depressive disorder (MDD**)		**Duloxetine 60 and 120 mg/day**				0.48		2.1 points for BPI average pain[87]
			Without MDD	594	-1.9(0.1)	388	-1.2 (0.1)	-.07		no	
			With MDD	203	-2.0(0.2)	147	-1.2 (0.2)	-.08		no	
Milnacipran											
Arnold, 2012[64] 2 doses	3 months	Mean weight change (kg)	**BMI** n/group		***Milnacipran 100 mg/day***				NR		NA
			<25 711	NR	-0.33(0.21)	NR	0.06 (0.20)	-0.39		NA	
			25-30 886	NR	-1.39(0.23)	NR	0.03 (0.24)	-1.42		NA	
			≥30 1507	NR	-1.48(0.21)	NR	-0.17 (0.19)	-1.31		NA	
			BMI		***Milnacipran 200 mg/day***				NR		
			<25 711	NR	-0.44(0.25)	NR	0.06 (0.20)	-0.50		NA	
			25-30 886	NR	-0.91(0.28)	NR	0.03 (0.24)	-0.94		NA	
			≥30 1507	NR	-1.13(0.26)	NR	-0.17 (0.19)	-0.96		NA	

* difference = change in outcome of (treated – control) per row Calculated by the MN EPC, not article authors. Positive difference indicates that placebo improved more than treated.

** calculated by the MN EPC from article text. Not directly reported by authors

1 kg = 1 kilogram=2.2 pounds; BPI-Brief Pain Inventory; FIQ stiffness-Fibromyalgia Impact Questionnaire stiffness subscale; MCID: minimum clinically important difference; NR: not reported; NA: not assessed; (MDD) Major depressive disorder; BMI: Body Mass Index; mg: milligrams; d: day; mo: month; tx: treated; c: controls; N-tx: number in treatment group; N-c: number in control group

Table 9. Fibromyalgia mixed-sample RCT treatment-by-subgroup interaction outcomes reported in the text*, by outcome measure

	Treatment	Author, Year	FIQ Total	FIQ Sub-scale	BPI Average Pain Severity	VAS Pain	PGI-I	HAMD	Other
Mixed sample RCTs (not pure subgroups)									
Pharmacologic									
	Duloxetine	Arnold, 2012[21]			a: NS s: NS r: Nonwhite $^{+}$> White p=0.017 d: NS g: NS				
		Arnold, 2010[25]					a: NS s: NS r: NS d: NS g: NS		
		Russell, 2008[24]**			a: NS s: NS r: NS d: NR		a: NS s: NS r: NS d: NR	d:NS within MDD strata	
		Arnold, 2005[23]			d: NS				
		Arnold, 2004[72] Primary: FIQ pain subscale	s: NS, p=0.101 d: NS, p=0.862	pain s: NS, p=0.121 d: NS, p=0.677	s: F $^{+}$> M, p=0.046 d: NR				s: F $^{+}$> M in Sheehan disability (p=0.007)
	Milnacipran	Gendreau, 2005[73]				d: NR			d: Mean pain scores on e-diary, Gracely or McGill pain questionnaires, NR
	Fluoxetine	Arnold, 2002[74]	d: NS	d: NS					
Psychological	Written emotional disclosure	Junghaenel, 2008[75]							3 composite measures for: c: pain, NS; c: fatigue, NS; c:psychological well-being: interpersonally distressed $^{+}$> adaptive coping, p=0.08. e: psychological well-being:

	Treatment	Author, Year	FIQ Total	FIQ Sub-scale	BPI Average Pain Severity	VAS Pain	PGI-I	HAMD	Other
									graduate educated $^{+}$> college or less educated
Mixed	multidisciplinary (MT) with/ without CBT	Lera, 2009[76]	f:MTCBT^{+} >MT in fatigued p=0.21 NS						f: MTCBT^{+}> MT on SF-36 emotional well-being in fatigued p=0.21 NS

Abbreviations: a=age; s=sex; r=race; d=depression, major depressive disorder (MDD) or history of MDD; e: education[75]; f: fatigue; g=generalized anxiety disorder (GAD); c: coping style[75]; w: SF-36 emotional well-being[76] o: other subgroup

CBT: cognitive behavioral therapy; MTCBT: multidisciplinary (MT) with CBT; NR: interaction significance was not reported; NS: Treatment by subgroup interaction not statistically significant; SF-36: Medical Outcomes Study short form 36 item health survey

+: the study reported statistically positive treatment effect in the subgroup for the outcome

>: improved more than

* no additional subgroup data provided in any articles except in Russell 2008

** Russell 2008 included text and table reporting of subgroup data.

Table 10. Summary of pooled RCT outcomes in fibromyalgia subgroups: significance of overall treatment-by-subgroup interaction terms where interaction results were reported (in text with/without p-values but without supporting data)

Treatment and Subgroup	Author, Year	Followup	FIQ	FIQ Subscales	BPI	VAS Pain	PGI-I	PGI-C	SF-36	Other
Pharmacologic										
Duloxetine										
Age (<55, ≥55)	Bennett, 2012[61]	3 months		**NS** p=0.246						
BMI (normal, overweight, obese, extreme obesity)	Bennett, 2012[61]	3 months		**NS** p=0.102						
FIQ Tiredness (mild, moderate, severe)	Bradley, 2010[62]	3 months	**NS** p=0.74	**NS** p>0.1	**NS** p>0.1		**NS** p=0.908		**NS** p>0.1	
MDD: Major depressive disorder	Arnold, 2009[63]	3 months	**NS** p=0.46		**NS** p=0.48 primary outcome		**NS** p=0.45		**NS** p=NR	**NS** (all) HAMD p=0.14 CGI-S p=0.98 SDS p=0.18 MFI p= NR
Milnacipran										
BMI (<25, 25-30, ≥30)	Arnold, 2012[64]	3 months								Weight loss **NR**
Baseline VAS Pain (≤64.7, >64.7)	Geisser, 2011[65]	3 months and 6 months				Reported % (n) with ≥30% improvement only **NR**		Reported % (n) with PGI-C ≤2 only **NR**	6 pt better in SF-36 PCS **NR**	≥30% better on PGI-C and VAS pain **NR**
Pregabalin										
Anxiety	Arnold, 2010[22]	Pooled 8, 13, and 14 weeks				**I**				HADS-A (≥2 pts, <2 pts) **I**
Depression	Arnold, 2010[22]	*Pooled 8, 13, and 14 weeks				**I**				HADS-D **I**
10 Comorbid Conditions	Bhadra, 2010[66]	*8-12 weeks						**NR**		Weekly pain rating of 0-10 **NR** all subgroups

Treatment and Subgroup	Author, Year	Followup	FIQ	FIQ Subscales	BPI	VAS Pain	PGI-I	PGI-C	SF-36	Other
Age (<40, 40-60, >60)	Byon, 2010[67]	* 8-14 weeks						**NR**		Weekly mean pain rating: greater pain reduction in older versus younger patients **NR**
Sex	Byon, 2010[67]	* 8-14 weeks						**NR**		Weekly mean pain rating: greater pain reduction in females versus males **NR**

Abbreviations: **BPI**-Brief Pain Inventory; **CGI-S**-Clinical Global Impression of Severity Scale; **FIQ**-Fibromyalgia Impact Questionnaire; **HADS-A**-Hospital Anxiety and Depression Scale, anxiety subscale score; **HADS-D**-Hospital Anxiety and Depression Scale, depression subscale score; **HAMD**-Hamilton Rating Scale for Depression; **I**-indeterminable as reported (figures, lack n's, etc.); **MFI**-Multidimensional Fatigue Inventory; **N**-not significant; **NR**-significance of interaction not reported; **NA**-not assessed; **PGI-C**-Patient Global Impression of Change Scale; **PGI-I**-Patient Global Impression of Improvement Scale; **SDS**-Sheehan Disability Scale; **SF-36**-MOS Short-Form 36-item Health Survey; **VAS**-Visual Analog Scale

* at least 1 of the pooled studies reported longest followup outcomes at less than 12 weeks

Table 11. Change in depression as measured by the Hamilton Depression Scale (HAMD) in one randomized clinical trial of duloxetine among fibromyalgia patients with MDD at baseline*

Author, Year	Group	Baseline HAMD with MDD	6 month change in HAMD with MDD
Russell, 2008[24]	Placebo	15.3 (4.58)	-4.8 (n=30)
	20 mg/day‡	15.1 (4.9)	-5.2 (n=22) 20→60 mg
	60 mg/day	15.4 (5.8)	-6.9 (n=30)
	120 mg/day	16.3 (4.4)	-7.2 (n=29)

* Authors reported baseline HAMD in patients without MDD, but did not report 6 month followup for those without MDD
‡: Duloxetine patients on the 20 mg dose during the first 3 months had their dose blindly increased to 60 mg/day for months 4 through 6 (n=49 [a]).

Table 12: KQ 1: Benefits of treatment: summary and strength of evidence of effectiveness and comparative effectiveness of treatments for fibromyalgia in adult subgroups

Population (FM subgroup)	Intervention/ Comparator	Outcome: Change from Baseline	Conclusion	Number of Studies	Strength of Evidence
With major depressive disorder (MDD)/ depression	Duloxetine	Brief Pain Inventory (BPI) average pain severity score	No evidence that treatment effects differ in subgroup	5: 4 RCTs; 1 pooled analysis*	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Patient Global Impression of Improvement (PGI-I)	No evidence that treatment effects differ in subgroup	3: 2 RCTs; 1 pooled analysis*	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Fibromyalgia Impact Questionnaire (FIQ) total score	No evidence that treatment effects differ in subgroup	2: 1 RCT; 1 pooled analysis*	Low (high risk of bias/many study limitations)
	Duloxetine	Hamilton Rating Scale for Depression (HAMD)	Unable to determine (impact of duloxetine on HAMD in adults with MDD and FM)	2: 1 RCT; 1 pooled analysis*	Insufficient (pooled interaction NS; RCT within stratum only)
Age	Duloxetine	BPI average pain severity score	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Sex	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (2 NS; 1 F improved >M)	3 RCTs	Low (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Race	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (1 NS; 1 NW improved >W)	2 RCTs	Low (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
With major depressive disorder/ depression	Milnacipran	Visual Analog Scale (VAS) for pain	Unable to determine (whether milnacipran effects on VAS pain differ in adults with MDD and FM)	2: 1 RCT (NR), 1 post hoc RCT analysis	Insufficient (outcomes reporting issues: 1 indirect, 1 incomplete)

Abbreviations: **F**: female; **FM**: fibromyalgia; **HAMD**: Hamilton Rating Scale for Depression; **M**: male; **MDD**: major depressive disorder; **NR**: not reported; **NS**: not significant; **NW**: nonwhite; **RCT**: randomized clinical trials; **W**: white

*Arnold 2009[63] pooled analysis of patient-level data from 4 RCTs is partially redundant with included RCTs (3 of 4 RCTs included in this report). Rationale for inclusion is provided in the report text

Discussion

Key Findings and Strength of Evidence

Limited, low strength of evidence for subgroup outcomes in adults with fibromyalgia suggests that patient subgroups do not have differential treatment effects compared with other adults with fibromyalgia. Overall treatment effects were small and even less when substantial placebo-group improvements were considered relative to treatment effects. Subgroup effects paralleled the magnitude and direction of overall treatment and placebo effects in mixed-sample studies, and absolute differences between treated and control subgroups were below MCID for the few studies where that could be determined. Reporting of overall interaction results, or assessment for differential treatment effects based on subgroup membership, was inconsistent across and within studies, and most interaction results were reported in text only.

There is a considerable lack of studies on subgroup treatment outcomes in the fibromyalgia literature to date. We found little evidence to inform treatment decisions for adults with fibromyalgia and complex psychological or medical comorbidities, since individuals with rheumatologic conditions, psychological disorders other than depression or anxiety, and serious medical conditions were uniformly excluded from clinical trials. Although older individuals were not excluded from clinical studies, very little information was reported on individuals over age 55, and extensive medical exclusion criteria likely impacted the participation of older individuals.

The fibromyalgia subgroup outcomes evidence to date is overwhelmingly pharmaceutical and based on highly selective sampling criteria, more than any other class of intervention we reviewed.

The pharmaceutical industry was heavily involved in the funding, study management, data, analysis, and reporting of results and it was common to find the corresponding and other authors located in industry (Appendix Tables E13-E16). Reporting of negative subgroup findings was often difficult to find and was sometimes indeterminable within carefully-selected article text. When reported, data tables most often presented p-values for individual comparisons within strata, rather than the overall negative subgroup interaction result.

In general, sample selection criteria were restrictive, and the extent to which such select patient samples reflect average patients in subgroups of adults with fibromyalgia is unknown. Despite this careful patient selection, attrition by 3-month followup was high. Dropouts were typically reported only in aggregate; the effects of attrition on initially small subgroup or even treatment group sample sizes were usually indeterminable. All but one study utilized the 1990 ACR preliminary diagnostic criteria for fibromyalgia.

Adverse effects were reported for subgroups only in one pooled analysis; these did not differ in subgroups. Subgroup samples were small except for in pooled analyses.

Other common findings were the lack of power calculations for subgroup effects, and corrections for multiple outcomes testing were rare. Also, it was not possible to determine whether or not subgroups were decided on a priori or post hoc in most studies.

The strength of evidence for assessing differential treatment effects in subgroups of adults with fibromyalgia is low or insufficient for all types of interventions (pharmacologic, physical, psychological, and mixed). Higher quality studies could change the conclusions of this review. Table 12 summarizes the major findings and associated strength of evidence for subgroup analyses with at least two studies. All but one comparison for which we could assign strength of

evidence involved duloxetine effects. Most compared those with and without major depression. All but one duloxetine comparison had low strength of evidence.

For pain, five studies showed no evidence that pain outcomes for adults taking duloxetine for fibromyalgia differ by their depression status.[21,23,24 63,72] Three studies of duloxetine showed no differences among subgroups on the Patient Global Impression of Improvement (PGI-I) measure.[24,25,63] Two showed no difference on the Fibromyalgia Impact Questionnaire (FIQ) total score with duloxetine.[63,72] Two others with insufficient evidence on duloxetine effects on the Hamilton Rating Scale for Depression did not provide sufficient information to assess the strength of the subgroup outcomes evidence (pooled interaction was not significant[63] and the RCT reported a within-stratum comparison only.[24])

For age, two studies with low strength of evidence found no differences on the BPI average pain severity score[21,24] and another two with low strength of evidence found no differences by age on the PGI-I.[24,25]

The studies of gender differences with low strength of evidence showed a mixed pattern with the BPI average pain severity score; in two there was no difference[21,24] but in one study females improved more than males.[72] When PGI-I was the outcome in two studies with low strength of evidence there was no treatment effect.[24,25]

Race showed mixed effects in two studies with low strength of evidence; in one there was no difference in BPI average pain severity by race[24] but in the other, non-whites improved more than whites in their BPI average pain severity scores.[21] The same two studies with low strength of evidence showed no difference by race when PGI-I was the outcome.[24,25]

Two studies addressed pain in patients with and without major depressive disorder who received milnacipran but did not report subgroup conclusions. The strength of evidence was insufficient due to outcomes reporting issues: one gave the proportion of 30 percent responders and one had incomplete reporting.

Applicability and Limitations of the Evidence Base

Several important characteristics limit the generalizability and applicability of these review results.

Study patients were largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ. Sample selection criteria were most restrictive for pharmaceutical studies so that adults with mental health conditions other than depression or anxiety, or those with higher medical comorbidity burden, were excluded. Adults with fibromyalgia and MDD were the most studied subgroup.

Nearly two-thirds of studies that reported subgroup effects were pharmaceutical trials and most assessed the effects of duloxetine. Fewer studies assessed the effects of physical interventions (such as exercise or weight loss), psychological interventions (such as CBT, psychotherapy or biofeedback) and very few assessed combination treatments.

Most drug trials were placebo-controlled RCTs. Other comparators included standard care, standard care plus adjunctive therapy, normal activities or education and information sessions.

Several issues affect the subgroup outcomes reported in this review. Outcomes are overwhelmingly reported for short term not long term outcomes, the latter of which is of greatest interest in the management of chronic fibromyalgia syndrome. The text on the magnitude of drug treatment effects for specific outcomes rarely acknowledged placebo group improvements that would have minimized the treatment benefits if they had been reported. We noted inconsistencies within and across studies in which subgroup interaction effects were reported, even when

methods sections identified that subgroup-treatment interactions were assessed. Selective reporting of subgroup outcomes was most often noted in results tables where individual within stratum comparisons were identified, but the overall interaction term was either not reported or reported only in text that was distant from the table. The effect of attrition within subgroups was missing so the extent to which studies could detect a difference even if one existed was not determinable, particularly since power calculations, when reported, were conducted to detect main not subgroup effects. Additionally, statistical corrections for multiple comparisons were either not conducted or not reported in most studies, raising the chance that significant differences in outcomes across groups, if present, may have been detected by chance alone. Although numerous outcomes measures were utilized, thereby limiting our ability to aggregate across studies, the range of type of outcomes assessed was not particularly broad. Multiple measures for pain were used. Pain, perceptions of global improvement, and changes in the overall the impact of fibromyalgia were most commonly reported; physical and social functioning were reported infrequently. Finally, industry funding and study involvement was considerable across all aspects of pharmaceutical trials including manuscript construction. Careful consideration for potential reporting biases cannot be overlooked in the context of outcomes interpretation from the included drug trials.

Given this contextual information, the extent to which the fibromyalgia subgroup literature from clinical studies to date reflects the breadth and severity of the broader population of adult subgroups with fibromyalgia is unknown, but complex patients with multiple physical and mental health comorbidities were most often excluded, which limits the applicability of these findings.

Limitations of the Comparative Effectiveness Review Process

The subgroup focus of this review necessitated some modifications to systematic review processes that are used to assess overall benefits and harms of treatments in average adults. In assessing risk of bias, we assessed typical risk of bias domains for RCTs, and added subgroup questions that were supported by the literature, which reflected common sense statistical practices for subgroup evaluation. We created a quality assessment form for observational studies and added similar subgroup items. We created quality assessment forms for pooled RCT IPD analyses that included quality assessments of the methods and reporting used for the summary analysis, and risk of bias assessments of the individual input RCTs. Although risk of bias/ study quality assessment is inherently subjective, we tried to evaluate quality as objectively as possible using prespecified forms that were uniformly used and rated by two reviewers.

We did not find evidence on all of our *a priori* subgroups, such as individuals with higher severity or longer duration of fibromyalgia, or rheumatologic conditions. Fibromyalgia duration and especially baseline severity as assessed with the FIQ were often part of the sample selection criteria for clinical trials, thereby excluding individuals with mild symptoms, mild impairment and/or shorter syndrome duration. Adults with rheumatologic conditions were routinely excluded from clinical trials.

Research Gaps

Despite the strong belief that the treatment for fibromyalgia may vary by subgroup, there is little information about its effect in subgroups. Many of the subgroups identified by experts to be of clinical interest were never investigated, or studied for only a few therapies. Where studies were done, the strength of evidence was low, suggesting that future research might change the

conclusions. Individuals with comorbid mental health conditions other than depression or anxiety, and/or those with higher medical comorbidity burden have been excluded from most clinical trials, especially drug trials. The extent to which such multimorbidity affects treatment needs, feasible treatment options and adverse effects requires further investigation to provide useful treatment information on these clinically complex adults. Individuals with comorbid rheumatologic and other autoimmune disorders are virtually missing from the general fibromyalgia treatment outcomes literature, and may require varied treatment approaches to successfully manage and accommodate both conditions.

Despite purportedly high utilization of multicomponent treatments for adults with fibromyalgia, few such studies reported on subgroup effects. Drugs studies dominated in volume of studies that assessed subgroup effects; far fewer studies assessed the effects of nondrug interventions that showed potential benefits.

The vast majority of studies are short term, leaving many questions about the durability of treatment effects in the management of this chronic condition. No study that reported subgroup outcomes assessed patients beyond 1 year.

Little is reported on functional outcomes in subgroups of patients with fibromyalgia, including physical and social functioning.

Potential differences in adverse effects in adult subgroups warrant more attention. Although most treatment harms were not serious, potentially differential effects in subgroups were reported in only 1 pooled IPD RCT analysis.

Transparently-reported, sufficiently powered clinical studies with a priori subgroup and hypothesis specifications were lacking, making subgroup treatment effect conclusions tenuous and limited. Efforts to reduce knowledge gaps from research involving fibromyalgia adult subgroups should aim to present findings that are clear and concise for clinicians to interpret.

Conclusions

Limited, low strength of evidence for subgroup outcomes in adults with fibromyalgia suggests that complex patient subgroups do not have differential treatment effects compared with other adults with fibromyalgia. Overall treatment effects were small and even less when substantial placebo-group improvements were considered relative to treatment effects.

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Abbreviations

ACR	American College of Rheumatology
AE	Adverse Events
AMED	Allied and Complementary Medicine
AS	Ankylosing spondylitis
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
BMI	Body Mass Index
CAM	Complementary and alternative medicine
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative effectiveness review
CES-D	Center for Epidemiologic Studies Depression Scale
CGI-S	Clinical Global Impression of Severity Scale
CHAMPS	Community Health Activities Model Program for Seniors
CNS	Central Nervous System
DBI	Dynamic Balance Index
DHEA	Dihydroepiandosterone
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder
EMG	Electromyography
EQ-5D	EuroQol health outcomes assessment
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FIQR	Revised FIQ
FM	Fibromyalgia syndrome
FSS	Fatigue Severity Scale
GAD	Generalized Anxiety Disorder
GI	Gastrointestinal
HAMD	Hamilton Rating Scale for Depression
HAQ	Health Assessment Questionnaire
HRQoL	Health-related quality of life
IBS	Irritable Bowel Syndrome
IPD	Individual patient data
ICTRP	International Controlled Trial Registry Platform
IGF	Insulin-like Growth Factor
IHAD	Iranian version of Hospital Anxiety and Depression questionnaire
IRGL	Impact of Rheumatic Disease on General Health
LPA	Lifestyle Physical Activity
LSEQ	Leeds Sleep Evaluation Questionnaire
MAF	Multidimensional Assessment of Fatigue
MCID	Minimal Clinically Important Difference
MDD	Major Depressive Disease
MeSH	Medical subject headings
MOS	Medical Outcomes Study sleep scale
MFI	Multidimensional Fatigue Inventory
MMPI	Minnesota Multiphasic Personality Inventory

MINI	Mini International Neuropsychiatric Interview
MPI	Multidimensional Pain Inventory
MT	Multidisciplinary Treatment
NR	Not Reported
NSAID	Non-steroidal Anti-inflammatory Drug
NSD	No Significant Difference
NW	Non White
OA	Osteoarthritis
PGART	Patient's Global Assessment of Response to Therapy
PGIC	Patient Global Impression of Change Score
PGI-I	Patient Global Impression of Improvement Scale
PHQ-8	Patient Health Questionnaire
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
QoL	Quality of Life
RCT	Randomized clinical trial
SCL-90-R	Symptom Checklist-90-Revised
SDS	Sheehan Disability Scale
SF-36	MOS Short-Form 36-item Health Survey
SLE	Lupus
SSRI	Selective Serotonin Reuptake Inhibitors
SNRI	Serotonin Nor-epinephrine Reuptake Inhibitors
TPs	Trigger Points
W	White
W_{max}	Maximal workload
WBV	Whole Body Vibration
VAS	Visual Analogue Scale
VO_2	Peak Oxygen uptake